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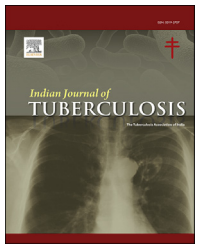

Original article

Indian Guidelines on Nebulization Therapy

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ABSTRACT

Inhalational therapy, today, happens to be the mainstay of treatment in obstructive airway diseases (OADs), such as asthma, chronic obstructive pulmonary disease (COPD), and is also in the present, used in a variety of other pulmonary and even non-pulmonary disorders. Hand-held inhalation devices may often be difficult to use, particularly for children, elderly, debilitated or distressed patients. Nebulization therapy emerges as a good option in these cases besides being useful in the home care, emergency room and critical care settings. With so many advancements taking place in nebulizer technology; availability of a plethora of drug formulations for its use, and the widening scope of this therapy; medical practitioners, respiratory therapists, and other health care personnel face the challenge of choosing appropriate inhalation devices and drug formulations, besides their rational application and use in different clinical situations. Adequate maintenance of nebulizer equipment including their disinfection and storage are the other relevant issues requiring guidance. Injudicious and improper use of nebulizers and their poor maintenance can sometimes lead to serious health hazards, nosocomial infections, transmission of infection, and other adverse outcomes. Thus, it is imperative to have a proper national guideline on nebulization practices to bridge the knowledge gaps amongst various health care personnel involved in this practice. It will also serve as an educational and scientific resource for healthcare professionals, as well as promote future research by identifying neglected and ignored areas in this field. Such comprehensive guidelines on this subject have not been available in the country and the only available proper international guidelines were released in 1997 which have not been updated for a noticeably long period of over two decades, though many changes and advancements have taken place in this technology in the recent past. Much of nebulization practices in the present may not be evidence-based and even some of these, the way they are currently used, may be ineffective or even harmful.

Recognizing the knowledge deficit and paucity of guidelines on the usage of nebulizers in various settings such as inpatient, out-patient, emergency room, critical care, and domiciliary use in India in a wide variety of indications to standardize nebulization practices and to address many other related issues; National College of Chest Physicians (India), commissioned a National task force consisting of eminent experts in the field of Pulmonary Medicine from different backgrounds and different parts of the country to review the available evidence from the medical literature on the scientific principles and clinical practices of nebulization therapy and to formulate evidence-based guidelines on it. The guideline is based on all possible literature that could be explored with the best available evidence and incorporating expert opinions. To support the guideline with high-quality evidence, a systematic search of the electronic databases was performed to identify the relevant studies, position papers, consensus reports, and recommendations published. Rating of the level of the quality of evidence and the strength of recommendation was done using the GRADE system. Six topics were identified, each given to one group of experts comprising of advisors, chairpersons, convenor and members, and such six groups (A-F) were formed and the consensus recommendations of each group was included as a section in the guidelines (Sections I to VI). The topics included were: A. Introduction, basic principles and technical aspects of nebulization, types of equipment, their choice, use, and

maintenance B. Nebulization therapy in obstructive airway diseases C. Nebulization therapy in the intensive care unit D. Use of various drugs (other than bronchodilators and inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy E. Domiciliary/Home/Maintenance nebulization therapy; public & health care workers education, and F. Nebulization therapy in COVID-19 pandemic and in patients of other contagious viral respiratory infections (included later considering the crisis created due to COVID-19 pandemic). Various issues in different sections have been discussed in the form of questions, followed by point-wise evidence statements based on the existing knowledge, and recommendations have been formulated.

Executive Summary

Introduction

Inhalational therapy today, not only happens to be the mainstay of treatment in obstructive airway diseases (OAD) such as asthma, chronic obstructive pulmonary disease (COPD), but is also used in a variety of other pulmonary and non-pulmonary disorders. Besides the bronchodilators and inhaled corticosteroids (ICS), several other drugs are now given through the inhaled route which include mucolytics, numerous antimicrobials, insulin, prostacyclin, surfactant, and non-steroidal anti-inflammatory drugs. It also facilitates systemic delivery through its large alveolar epithelial surface thus helping in rapid drug absorption to be utilized in some systemic disorders.

Besides pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI), nebulizer is also used as an aerosol generator in which the formulated drug in aqueous solution or suspension is atomized into droplets making it a useful drug delivery system in emergency and critical care setting, besides for some patients for home use as well. Nebulization has also got to play a great role in paediatric patients. National and International guidelines for the management of asthma, COPD and other pulmonary disorders often recommend the use of nebulization to administer drugs to the lungs. However, it is recognized that much of this practice may not be evidence-based and some of these practices in their current use may be ineffective or even harmful. It has also been observed that often the dose delivered to the lung can increase over ten folds just by changing from a poor nebulizer system to a highly efficient one.

Considering paucity of proper guidelines on the usage of nebulizers in acute and domiciliary settings, National College of Chest Physicians (India), is embarking on a scientific initiative to study and review the scientific and clinical principles of nebulized therapy and to produce a set of evidence-based guidelines on its use. These guidelines will cater to patients and health care personnel involved in nebulization practices, to have an overall improvement in the clinical use of this therapy, enhancing both its efficacy and safety. It will provide a comprehensive approach on the use of this therapy in various disease conditions, using different medications, in different settings, using various techniques of use, and assessing the relative benefits of different available equipment. It will also serve as an educational and scientific resource for healthcare professionals, and to promote future research by identifying neglected and ignored areas in this field. Such comprehensive guidelines on this subject have not been available in the country and the available international guidelines have not been updated for an exceptionally long time though so many changes are taking place in this field.

This guideline is based on all possible literature that could be explored with the best available evidence and incorporating expert opinions. To support the guideline, a systematic search of the electronic databases was performed to identify relevant studies published. Rating of quality of evidence and strength of recommendation was done using the GRADE system. Topics identified for preparing guidelines were as below:

GROUP-A (Section-I): Introduction, basic principles and technical aspects of nebulization, types of equipment, their choice, use, and maintenance.

GROUP-B (Section-II): Nebulization therapy in obstructive airway disease.

GROUP-C (Section-III): Nebulization therapy in intensive care unit.

GROUP-D (Section-IV): Use of various drugs (other than bronchodilators & inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy.

GROUP-E (Section-V): Domiciliary/home/maintenance nebulization therapy; and public and health care workers education.

GROUP-F (Section-VI): Nebulization therapy in COVID-19 pandemic and in patients of other contagious viral respiratory infections.

Various issues in different chapters have been discussed in the form of questions. In the answer to each question, discussion based on existing knowledge followed by point wise evidence statements and recommendations have been provided.

The last group-F (Section-VI) was added at a later stage, considering the crisis created due to the COVID-19 pandemic, which has raised several questions and doubts, related to nebulization, in terms of risk of infection to healthcare professionals and others. Table 1 Fig 1 Table 2

Section - I (Group - A): Basic principles and technical aspects of nebulization; types of equipment, their choice, use, and maintenance

Section-1 (Group-A) of the guidelines has been dealt under three parts as shown below:

- Part-1: Basic principles and technical aspects of the nebulization
- Part-2: Types of nebulizer equipment, their choice, and use
- Part-3: Maintenance of Nebulizer Equipment

PART 1: Basic principles and technical aspects of the nebulization

Practical definitions

Mass Median Aerodynamic Diameter (MMAD)

The diameter of a sphere of unit density that has the same aerodynamic properties as a particle of median mass from the aerosol.[13]

The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.[14]

Mass Median Diameter

The diameter of the particle such that half the mass of the aerosol is contained in smaller diameter particles and half in larger.[13]

Geometric Standard Deviation (GSD)

The GSD measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at 1 SD (s) from the median diameter. In a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter. Aerosols with a GSD of 1.22 are considered polydisperse. Most therapeutic aerosols are polydisperse and have GSD in the range of 2-3. It is denoted as sg or GSD.[14]

Aerosol Output

Mass per minute of particles in aerosol form produced by the nebulizer.[13]

Respirable Particles

Particles <5 μm aerodynamic diameter (13).

Respirable Fraction

The mass of respirable particles expressed as a percentage of the aerosol output.[13]

Respirable Output

Mass of respirable particles produced per minute (aerosol output × respirable fraction).[13]

Drug Output From The Nebulizer

The mass of drug produced per minute as an aerosol.[13]

Residual Volume

This is the volume of liquid remaining in the nebulizer reservoir when nebulization has ceased. It will affect the drug output from a given fill volume.

If the residual volume is less than 1.0 ml, a fill volume of 2.0-2.5 ml may be adequate; nebulizers with residual volume of more than1.0 ml generally require fill volumes of about 4 0 ml.[13]

Fill Volumes

The amount of drug solution or suspension filled in the nebulizer reservoir chamber. Nebulizer chambers have different maximum fill volumes; the volume of drug solution must be known not to exceed the maximum fill volume.[13]

Volume output from the nebulizer

The volume of solution leaving the nebulizer chamber. The nebulizer output is traditionally calibrated by weighing the nebulizer unit before and after activation, assuming that no solvent is lost during nebulization by evaporation, which is not correct, invalidating this assumption. The volume output whilst useful as a general guide to nebulizer performance, it does not give precise information about the actual drug output.[15,16]

Driving gas

Air can be used as driving gas except for acutely ill asthmatic patients where oxygen may be used. COPD patients should ideally receive monitored oxygen therapy while using an air-driven nebulizer system (to avoid increasing carbon dioxide (CO2) retention).[14]

Flow rate through the nebulizer:

The flow rate of gas, whether from a compressed source or from a compressor, that drives the nebulizer chamber. It is not the same as the flow rate from the compressor, which will often be considerably higher. It is obtained by producing a pressure-flow rate curve for the nebuliser. Recordings of circuit pressure are made from zero flow (maximum pressure) to maximum flow (minimum pressure) using a rotameter, a compressor unit (or flow generator), and pressure measuring device. By substituting the nebulizer chamber for the rotameter the pressure in the circuit can be obtained with a constant flow rate from the flow generator. From the pressure-flow curve the flow rate at the nebulizer can be obtained.[17]

Aerosol

A relatively stable suspension of liquid droplets or solid particles in a gaseous medium.

Coarse particles: 1-10 μm.

Fine particles: 0.1 −1 μm.

Ultrafine particles: < 0.1 μm.

Fume

An aerosol of solid particles, generally less than 0.1 μm in size, that arises from a clinical reaction or condensation of vapours, usually after volatilization of molten materials.

Questions related to Part 1:

Q 1. What is the ideal particle size for nebulization?

Evidence Statement:

- The ideal 'particle size', generated by a nebulizer, depends upon the desired target site of action of the drug.
- Smaller particle sizes (MMAD< 2μm) have increased peripheral lung deposition while larger particles are associated with increased central airway deposition.
- Though smaller particles achieve greater total lung deposition, larger ones are more efficacious and produce greater bronchodilation (MMAD ranging between 3 and 6 μm). For

drugs requiring peripheral intrapulmonary deposition (antimicrobials), ideal aerosol MMAD will be < 2 μm.

Recommendations:

- The ideal particle size during nebulization in a case is variable and is dependent on the target site of action of drugs to be delivered to the airways. (II A)
- The ideal aerosol MMAD recommended, while using bronchodilators in OAD, is between 3 and 6 μm. Though smaller particles achieve greater total lung deposition, the larger particles are more efficacious achieving greater bronchodilation (II A)
- For drugs requiring peripheral intrapulmonary deposition (antimicrobials), ideal aerosol MMAD recommended is < 2 μm. (II A)

Q 2. How does the flow rate, fill volume & nebulization time affect drug output?

Evidence statement:

- Flow rate, fill volume, and nebulization time influence the production of aerosols of respirable MMAD.
- High flow rates of 6 to 8 L/min are associated with the generation of higher number of particles with MMAD in the respirable range in a short nebulization time. In case of antibiotics, using greater volume fill and higher flow rate markedly increased the intra pulmonary deposition of the drug.
- Higher fill volumes of 4 to 6 ml are associated with better MMAD particle size in respirable range but with a longer nebulization time. **A** nebulization time of up to 10 minutes is optimal or up to the point of sputtering.
- Different makes of nebulizers are associated with variable performance for a given flow rate, fill volume, nebulizer solutions, and may influence the duration of nebulization. Nebulizer reservoir bags are useful to attain higher doses and utilization of expensive medications more efficiently.

Recommendations:

- It is recommended that flow rate and fill volumes of a nebulizer must be mentioned by the manufacturer which should be taken into cognizance by the user to optimize the performance of nebulizers. (III A)
- It is recommended that a minimal fill volume of 4 - 6 ml and a flow rate between 6 – 8 L/min using compressed air may be used for obstructive airway disorders in the absence of recommendation by the manufacturer. (III A)
- The optimal nebulization time recommended is up to 10 minutes or until spluttering occurs. (III B)
- Nebulizer reservoir bags may be useful to attain higher doses and for utilization of expensive medications more efficiently. (III B)
- It is recommended that higher flow rates between 8 – 10 L/min and greater fill volumes may be used for administration of antibiotics targeting intrapulmonary deposition. (III A)

PART-2: Types of nebulizer equipment, their choice, and use

Q 1. What are the types and technical details of nebulizers available including their mechanism of function and comparative evaluation?

Evidence statement:

- Three types of nebulizers are available: Pneumatic or Jet, Ultrasonic and Vibrating Mesh Nebulizers (VMN), all having different mechanisms of function.
- Ultrasonic nebulizers are not suitable for use in suspensions, liposomes, viscous solutions, and proteins; besides their having large residual volumes.
- The technical details and comparison between different nebulizers are given in a tabular form.
- Jet nebulizers are simple, inexpensive, and commonly used, whereas vibrating mesh nebulizers are more efficient but expensive.

Recommendations:

- Choice of nebulizer is to be made between Jet, ultrasonic and vibrating mesh nebulizers according to the usage in patients (Grade IIIA)
- Jet nebulizers are recommended for common use, whereas ultrasonic nebulizers have limited uses, but vibrating mesh nebulizers are more efficient but expensive. (UPP)

Q 2. How do you compare different types of nebulizers?

Evidence statement:

- The newer nebulizers like the ultrasonic and the vibrating mesh nebulizer have higher efficiency compared to the conventional jet nebulizer, with shorter nebulization time and smaller residual volumes.
- Changes in the temperature and concentration of the drug in the reservoir may occur with jet and ultrasonic nebulizers which can influence the droplet size during nebulization.
- Mesh nebulizers have a higher drug delivery and better drug bioavailability in comparison to jet nebulizers requiring reduction in the dosages of the drugs to prevent the adverse events and its loss.
- The mesh nebulizer compared to the jet, shows improved delivery and better efficiency of bronchodilators among asthmatics reducing their admission rates and the median length of stay in the emergency department.
- Positioning of the nebulizer in the ventilator circuit in mechanically ventilated patients influences the efficiency of nebulizers and this position is variable with different nebulizers.

Recommendations:

- All the three nebulizers in the clinical practice; jet, ultrasonic, and mesh; are efficacious in the appropriate clinical scenarios and it is recommended to make a choice according to the clinical situations. (UPP)

- Mesh nebulizer is recommended as the most efficient device in terms of relative efficiency with a shorter nebulization time, smaller residual volumes, and not leading to any change in the temperature of the drug during nebulization. (II A)
- While using the mesh nebulizer, the dosage of the drug may need to be reduced and the patient be more closely monitored for the clinical response and any adverse effects due to overdosages. (II B)
- The position of nebulizers in the ventilator circuit, for their proper efficiency, is variable with different nebulizers which must be followed during usage. (II A)

Q 3. Which nebulizers are suitable for drugs other than bronchodilators and inhaled steroids?

Evidence statement:

- Vibrating mesh nebulizers effectively nebulize solutions and suspensions; as well as liposomal formulations; proteins, such as α-1 antiprotease, dornase alfa; and antibiotics.
- Denaturation of non-complexed, supercoiled DNA occurs during nebulization while using mesh nebulizer which is like jet nebulizers.

Recommendations:

- The vibrating mesh nebulizer is recommended to be used to deliver a wide range of solutions and suspensions; including liposomal formulations; proteins, such as α-1 antiprotease, dornase alfa; and antibiotics. However, it can also denature non-complexed, supercoiled DNA, like jet nebulizers. (III B)

(Please also refer to Q. No. 8; Part II of Group-A for more information).

Q 4. What relevance do jet nebulizer and compressor combinations have?

Evidence statement:

- The available jet nebulizer can have variable performances and changing the nebulizer and the compressor combination can change the flow-pressure and aerosol characteristics. Users should be cautious when changing compressor/nebulizer pairs unless they are aware of the resulting impact on the flow-pressure and aerosol characteristics.
- It has been seen in bench studies that the long-term use of compressor/nebulizers can affect their performance.

Recommendations:

- The compressor nebulizer combination recommended by the manufacturer should be used since any variation may alter their performance. (III B)
- There is a need to check the clinical performance of the nebulizer on regular intervals with their continued use. (UPP)

Q 5. How do we select the type of machine? What are the points to be considered while choosing a nebulization device?

The appropriateness of a nebulizer for a patient in each clinical situation depends on several factors. Following points need to be considered before making a choice in a particular patient.

- In what formulation is the drug available? Is it in a solution or a suspension form?
- Compare its working in terms of ease of use and safety?
- The output characteristics, efficiency and performance of the nebulizer must be assessed before the selection.
- Is the device patient-friendly in terms of its operation and maintenance?
- Is the device clinically useful on a broad application (can it be used to treat different patient populations in various clinical settings and patients in different age-groups)?
- Is the device cost effective and is it reusable?
- Can the device be used for many drugs?
- Is the device eco-friendly in terms of environmental contamination

The device selection may be done with the help of suggested algorithm (Fig. 1).

Q 6. What are the quality standards available for the nebulizer performance?

Evidence statement:

- Various standards have been formulated by different organizations for the quality control purposes and providing technical details to guide the selection of proper equipment and provide proper instructions of its use, however, presently, International Organization for Standardization [ISO] 27427:2013[E]) seems most appropriate amongst all others.
- The parameters laid down by ISO to maintain these standards include 'Delivered Dose' (DD) and 'DD-output rate', under in vitro laboratory conditions, represent a good basis for the direct comparison of nebulizers commercially available.
- However, not including 'Respirable DD' (RDD) - the amount of drug contained in droplets of a size suitable for penetration into the lungs (<5 μm), in these parameters, is a limitation.
- It has also been emphasised by ISO that "the percentage of fill volume emitted is an important value to be disclosed to the user, since it influences the decisions of dosage intended for delivery in terms related to the expected amount of drug given to the patient."
- Though the results of the test methods in the standards have limited clinical usefulness, at least these need to be made mandatory for the manufacturers to follow and make relevant declarations to guide the physicians/users in making a correct choice and its proper usage.

- There is significant variance in DD or RDD between different brands of non-breath-actuated nebulizers and to some extent between jet and mesh nebulizers.

Recommendations:

- While making a choice of nebulizer, preference be given to those manufacturers who comply with the standards of ISO, CEN, USP, or EP; preferably ISO; and who have made declarations of the technical details on their products, as per the guidelines of that particular organization. (UPP)
- It needs to be made mandatory for the manufacturers to follow these guidelines and make relevant declarations on the product to guide the physicians/users of making a correct choice and its correct usage. (UPP)
- Nebulizers without the declarations need to be tested for required parameters before use (UPP)

(Please also to refer to Q. No. 2; Part I of Group-A for additional information).

Q 7. What different solutions/suspensions are suitable to be administered by the different machines?

Evidence statement:

- Most of the nebulized drugs are available either in solution or suspension form. The drug dispersion in droplets generated may be more homogenous with solutions but not so with the suspensions.
- The ultrasound nebulizer is ineffective in nebulizing drugs which are in suspension forms (such as budesonide).
- The aerosol characteristics and nebulization efficiency have been shown to depend on the physico-chemical properties (viscosity, density, surface tension and ion concentration) of the drug solution and these effects are more pronounced with the use of mesh nebulizers.
- Mesh nebulizer is unable to perform optimally at high viscosity.

Recommendations:

- The drug dispersion in the aerosol generated on nebulization is more homogenous with solutions than suspensions (III A)
- The use of an ultrasound nebulizer is not recommended for the drugs in suspension form. (II A)
- Clinician and researchers should recognize that changes in the physico-chemical properties (viscosity, density, surface tension and ion concentration) of the drug solution may impact the nebulizer output and aerosol characteristics (III B)
- It is recommended to use the jet nebulizer if the viscosity of the solution is not known. Mesh nebulizers are not suitable for solutions with high viscosity (UPP)

Q 8. What are the problems related to mixing various drug formulations in the nebulizer cup?

Evidence statement:

- Mixing of drugs for convenience is a common practice, even if prescribed for separate administration. The physicochemical compatibility of mixed nebulizer solutions and suspensions must be ensured before doing so.
- Mixtures of inhalation medications are designated as physicochemical compatible, when chemical stability ($\leq$10% degradation) of each active substance is maintained with unchanged pH values, osmolality, and physical appearance over a test period of $\leq$24 h.
- Potencies of antibiotics in inhalation mixtures are determined by fluorescence immunoassay (tobramycin) or by using the 'Microbiological assay of antibiotics' (agar diffusion assay)
- Coadministration of different drugs can impact the aerosol characteristics and its output from a nebulizer. Incompatibility and/or instability of the medication mixtures can lead to impaired drug safety and/or reduced potency and efficacy up to treatment failure.
- Variations are seen in the aerosol MMAD; geometric standard deviation (GSD); respirable fraction (RF%); respirable mass (RM) with different drug admixtures and with different machines.
- The combination of the drugs may result in loss of potency if there is a delay in administering the solution.
- Many nebulizer drugs are mixable without provoking incompatibilities. However, even certain excipients used could be identified as a reason for incompatibilities, such as impaired activity of dornase alfa.
- Information has been provided in the table on compatibility of mixing drugs and this is based on their in vitro studies and a thorough literature search.
- Aero-dynamic characteristics after nebulization of mixtures also need to be studied. Such studies assessing these characteristics on compatible mixtures, nebulized with commonly used nebulizers, are limited and need to be encouraged.
- The clinical efficacy of simultaneous inhalation of duplicate, tripartite or quadripartite mixtures must be evaluated in clinical studies before final recommendations for the inhalation regimens can be made.

Recommendations:

- Mixing of drugs of various formulations in the nebulizer cup is recommended only to be done once the physicochemical compatibility of the combination is ensured. (III A)
- Mixtures that show change in colour or odour, or presence of haze and precipitation are designated as incompatible and should not be used. However, lack of physical incompatibility does not rule out chemical decomposition (III A)
- Only those mixtures are recommended to be used where chemical stability ($\leq$10% degradation) of each substance has been shown and where pH value, osmolality; and physical characteristics are shown to be maintained over a period of $\leq$24 hours. (III A)
- Co-administration of different drugs can impact the aerosol characteristics, nebulizer output, aerodynamic properties, stability, potency, and safety of the individual drugs. Hence, mixing of drugs is only to be done where these factors have been ascertained (III A)

- Excipients present in the drug formulation also need to be considered while combining drugs since these have also been identified as reasons for incompatibilities even if the active drug remains to be the same (III A)
- It is recommended to use freshly prepared mixtures of compatible drugs as delay in administration may result in loss of potency of constituent drugs (III A)
- Some preliminary recommendations, based on the literature available, on mixing of some of the drugs are given in the table, may be utilized for clinical purposes (UPP)
- It is recommended to carry out in vitro and clinical studies, which so far are limited, on compatible mixtures of 2 – 4 drugs, to find out their impact on the nebulizer output, aerosol characteristics, aerodynamic properties, and clinical efficacy of the drugs, before a final recommendation can be made. (UPP)

Q 9. What are the different types of interfaces available for aerosol delivery to lungs during nebulization and how do they compare with each other?

Evidence statement:

- Multiple types of interfaces are available for use with nebulizers including mouthpiece, facemask, nasal mask, pacifier mask, high-flow nasal cannula and the hood. The mouthpiece allows for efficient drug delivery to the lung as compared to the face mask.
- Face masks are often associated with leakage of aerosol leading to significant facial and eye deposition This risk is mitigated by using a mouthpiece and the incidence of adverse events including glaucoma while using bronchodilators are reduced.
- Multiple types of face masks are available commercially (Dragon face, fish face, standard nebulization mask, valved mask). The design characteristics of the mask can influence the drug delivery, with the fish mask having higher inhaled mass. The distance between the face and the mask does not make any difference.
- The front-loaded masks (aerosol enters the facemask in front of the mouth) are more efficient than the bottom-loaded masks (aerosol enters the facemask from below the mouth) but these may produce greater facial and ocular deposition.
- Loose application of the interface decreases the drug delivery from the nebulizer and leads to wastage of the drug.
- Wearing nose clips while using a mouthpiece, has shown variable results in terms of aerosol delivery to the lungs and can be uncomfortable too.
- The occlusion of the holes (exhalation port) of the face mask do not increase the amount of drug delivered.
- Using a valved mask increases the drug delivery to the lungs.

Recommendations:

- Mouthpiece is recommended as the preferred interface over face masks having improved drug delivery during nebulization therapy. The drug deposition on the face and eyes, which is significant with face masks, is also eliminated with its use (II A)
- Use of a mouthpiece as against a facemask is particularly recommended when high doses of anticholinergics are used to avoid risk of glaucoma or blurred vision. It is also to be preferred when inhaled steroids are to be administered (III B)
- The choice of the interface should also be based on the convenience to the patient. Acutely ill patients, infants and young children who find it difficult to use a mouthpiece may use a facemask (UPP)
- The design of face masks has an influence on drug delivery, however, the distance between the face and the mask does not make any difference. (III B)
- The front-loaded face masks are preferred in comparison to the bottom-loaded masks for better drug delivery, however, to minimize drug deposition on the face and eyes while using anticholinergic drugs., a bottom-loaded face mask is preferred. (III B)
- Wearing a nose clip with a mouthpiece is not recommended, being uncomfortable to the patient, and its role in improving the drug delivery is also uncertain. (III B)
- A proper fit and an adequate seal of the mask must always be ensured. The occlusion of the holes on the face mask does not improve drug delivery. However, use of a valved-mask is recommended for better drug delivery (III B)

Q 10. What is 'The blow by' technique of administering inhaled nebulized therapy and how useful is it?

Evidence statement:

- The 'blow by' technique, used in uncooperative children, is directing the aerosol plume towards the patient's face while keeping the nebulizer away from the child.
- The blow by technique reduces efficacy as it does not ensure effective drug delivery and is mostly wasteful.

Recommendation:

- The use of the blow by technique is not recommended for use. (III A)

Q 11. What are 'Pacifier masks', and how useful and efficient are they?

Evidence statement:

- Face masks are often not accepted by infants due to their non-cooperative nature and crying habits leading to reduced aerosol deposition to the lungs.
- 'Suckling' on a pacifier mask often calms the infants, hence, a face mask incorporating a pacifier is more acceptable to them. This allows the child to keep suckling the pacifier while the nebulization is being done allowing prolonged nebulization time.
- Using a pacifier during aerosol treatment in infants makes it as efficient as treatment with conventional masks besides having the calming effect. The design of

the mask also allows an optimal seal and minimal dead space.
- Infants are preferential nose breathers and with a pacifier in mouth they inhale aerosols through their nose only. This may affect the drug delivery to the lungs since nose has the highest airflow resistance and it also filters the particles effectively.

Recommendation:

- The pacifier equipped masks are recommended to be used to deliver nebulized drugs to infants while they continue suckling making it more acceptable besides having aerosol deposition similar to a conventional mask. (III A)

Q 12. Can nebulization be done through high flow nasal cannula (HFNC)?

Evidence statement:

- The high flow nasal cannula circuit (HFNC) allows effective aerosol drug delivery to the lungs.
- There was no benefit of using heliox (80/20% mixture of helium and oxygen) against oxygen in delivering aerosols to the lungs.
- The position of the nebulizer in the circuit, the adapter used, size of cannula, and the type of HFNC system may impact the delivery of drugs.
- Aerosol delivery can be done via HFNC, bubble CPAP, and synchronized inspiratory positive airway pressure (SiPAP) devices. Placement of the nebulizer prior to the humidifier is a preferable position

Recommendations:

- The high flow nasal cannula (HFNC) circuit, when in use, in the emergency department and the intensive care unit, is recommended to be utilized for the nebulized therapy having high efficiency. (III B)
- Use of heliox during nebulization through HFNC does not provide any additional benefit. (III B)
- Various factors such as position of nebulizer in the circuit, adapter use, the size of cannula, and the type of HFNC system, influence the drug delivery. Placement of the nebulizer prior to the humidifier is a preferable position (III B)
- Besides HFNC aerosol delivery can also be effectively done via other devices such as bubble CPAP, synchronized inspiratory positive airway pressure (SiPAP) and nasal high flow (NHF). (III B)

Q 13. How useful is the 'hood interface' for aerosol therapy amongst neonates and infants?

Evidence statement:

- The hood interface is an enclosure that covers the head and neck of a neonate or infant to deliver aerosol to the lungs while isolating them from the ambient air.
- The 'hood' is an effective interface for delivering aerosol therapy to neonates and infants and is as efficient as a facemask while having a better therapeutic index.
- The face-side position has less facial-ocular deposition than the face-up position, while still achieving similar lung delivery efficiency.
- The hood interface provides better tolerability and is less time consuming than a mask.

Recommendations:

- The 'hood interface' is recommended as an efficient and effective technique for administering aerosol therapy to neonates and infants with better tolerability and therapeutic index than face mask, besides taking lesser nebulization time. (II A)
- Preference be given to hood interface over other masks while administering aerosol therapy to neonates and infants (II B)
- 'Face-side' position in 'hood interface' is the preferred position than face-up position, having similar lung delivery with less facial-ocular deposition (II A)

Comparison of the various interfaces

Comparison of various interfaces has been provided in the table mentioning their description, its advantages, and disadvantages along with suggestions for the best use:

PART 3: Maintenance of Nebulizer

Q 1. What are the components of various kinds of nebulization machines?

Evidence statement:

- Details of different machines and the components of all the three types of nebulizers: jet, ultrasonic, and mesh, have been shown and the components requiring frequent replacements have been mentioned.
- The pneumatic jet nebulizer comes in four different designs; ultrasonic nebulizer as small and large volume; and mesh nebulizer in active or passive vibrating forms.
- The four different types of pneumatic jet nebulizer include: jet nebulizer with reservoir tube, jet nebulizer with collection bag, breath-enhanced jet nebulizer, and breath-actuated jet nebulizer (manual breath actuated, mechanical breath actuated and microprocessor breath actuated). These newer nebulizers are designed to minimize aerosol loss during exhalation.

Recommendations:

- It is recommended to increase awareness about different types of nebulizers and their components for its proper usage, performance and maintenance. Some of the components of these nebulizers need to be regularly replaced (UPP)
- Among the jet nebulizers, the newer designs are recommended for improved drug delivery and lesser contamination of the ambient air by reduction in wastage of the aerosol. (UPP)

Q 2. What are the steps in using the nebulizer?

Evidence statement:

- Instructions for the assembly and use of the equipment, filling up of the nebulizer chamber, and precautions to be taken, have been given in detail.

Recommendations:

- Recommended steps to assemble equipment, filling up of nebulizer chamber, correct use of nebulizer, and precautions required must be followed for proper aerosol therapy (UPP)
- Patients with acute asthma are recommended to be nebulized with oxygen driven equipment, whereas those with COPD by air driven equipment (UPP)

Q 3. What steps are to be taken while storing a nebulizer?

Evidence statement:

- Instructions for proper cleaning and storage of the equipment are mentioned.
- Servicing and maintenance checks need to be followed as per manufacturer's instructions.

Recommendations:

- Nebulizer is recommended to be thoroughly cleaned, dried, and disinfected before storage as per manufacturer's instructions (UPP)
- Manufacturer's instructions should be followed for proper servicing and maintenance checks of the equipment. Single-use devices should not be re-used. (UPP)

Q 4. How to clean and disinfect the nebulizer and maintain infection control?

(Please also see the information given in Section -E or Chapter-V).

i) **What is the rationale for cleaning and disinfecting?**

Evidence statement:

- The CDC guideline for disinfection and sterilization in healthcare facilities, (2008), categorises nebulizer in "Semi critical medical devices" and recommends its proper cleaning, disinfection, rinsing, and air drying after each use.
- Nebulizers have been documented as a frequent and potential source of bacterial contamination and colonization and have been linked with nosocomial infections in the hospital.
- Proper rinsing and drying of the nebulizer after cleaning and disinfection is important before storage since bacteria grow in wet and moist places. The drying is enhanced by attaching gas flow after rinsing.
- The performance of the nebulizer may change in time, if not cleaned, maintained, and disinfected properly. The hospital staff and patients need to be made aware of the importance of these.

Recommendations:

- Proper cleaning and disinfection of nebulizers is recommended to be done after each use to prevent bacterial contamination and colonization leading to nosocomial infection. Instructions given by the manufacturer must always be incorporated. (UPP)
- It is also recommended that nebulizers should be thoroughly dried and stored in a clean dry place between treatments. (UPP)

ii) **What are the methods available for cleaning?**

Evidence statement:

- Proper cleaning, disinfection, and drying of the nebulizer is done after disassembling the parts and removing the tubing which is not washed
- Cleaning and disinfection are done after every use with sterile water, however, when done once or twice a week, the washing of parts is done with warm water and liquid soap. Final rinse is to be done with sterile water.
- Manufacturer's instructions must also be followed in the maintenance of the equipment.

Recommendations:

- Cleaning of nebulizer after each use is recommended to be done using sterile or distilled water. When cleaning once or twice a week, use liquid soap for thorough washing and use sterile water for the final rinsing. Manufacturer's instructions must always be followed for dis-infection. (III B)

iii) **What are the agents available for disinfection and what are the other disinfection methods?**

Evidence statement:

- Disinfection of nebulizer is done after each cleaning to reduce the chances of bacterial contamination.
- Various disinfectants used to sterilize the equipment include: 70% isopropyl alcohol (soaking for 5 min.); 3% hydrogen peroxide (soaking for 30 min.); boiling (5 min.); 1-part white vinegar in 3-parts hot water (soaking for 1 hour); solution of 1-part household bleach and 50-parts water (soaking for 3 min.)
- Nebulizer can also be disinfected by boiling or microwave heating for 5 minutes or by washing in a dishwasher (at a temperature of >158°F or 70°C) for 30 minutes.
- Follow manufacturer's guidelines for cleaning and disinfection to maintain integrity and proper functionality of the equipment.

Recommendations:

- Regular disinfection after cleaning of the nebulizer is recommended after each use to prevent bacterial contamination and colonization in the equipment. (UPP)
- Disinfectants recommended for soaking nebulizer include use of one of the following: 70% isopropyl alcohol for 5 min, 3% hydrogen peroxide for 30 min, white vinegar and hot water in 1:3 ratio for 60 min, household bleach in water in 1:50 ratio for 3 min. (III A)
- Disinfection is also recommended by simply boiling the nebulizer for 5 min. or by microwave heating for 5 min. or by washing in a dishwasher (at a temperature of >158°F or 70°C) for 30 min. (III A)
- Manufacturers guidelines for cleaning and disinfection must always be followed for proper functioning of the equipment.

iv) **How frequently should the nebulizer be cleaned?**

Evidence statement:

- Unclean and dirty nebulizers become a source of infection through colonization of microbes in it.
- Dirt can be difficult to clean if allowed to dry and stay long if not cleaned on a regular basis.
- Ideally parts of nebulizer should be cleaned after every treatment to help reduce the risk of infection.
- Proper care be taken to avoid damage to the nebulizer parts during cleaning.

Recommendations:

- It is recommended to clean and disinfect the nebulizers after every use, not allowing the dirt to dry up and stay long, making it difficult to clean. Caution needs to be observed to be gentle while cleaning to avoid damage to the parts. (UPP)

V) **Are there any specific instructions for the vibrating mesh (VMN) and ultrasonic nebulizers?**

Evidence statement:

- Vibrating mesh and ultrasonic nebulizers should be cleaned and disinfected according to the manufacturer's recommendations only.
- The mesh in the vibrating mesh nebulizers is not to be touched during cleaning to avoid damage to it leading to malfunctioning of the equipment.

Recommendations:

- It is recommended to follow manufacturer's instructions and recommendations for proper cleaning and disinfecting the vibrating mesh and ultrasonic nebulizers avoiding any damage to the equipment. (UPP)
- Avoid handling of the mesh in VMN to prevent malfunctioning of the equipment. (UPP)

SECTION - II (Group - B): Nebulization therapy in obstructive airway diseases

For patients suffering from the obstructive airway diseases (OAD), inhalation of aerosolized medications e.g., bronchodilators and corticosteroids continue to be the most important therapy. Although inhalation therapy with hand-held inhalers is more common, nebulizers are also widely used. These are relatively easier to use with the benefits of requiring minimal inspiratory flow, hand-breath coordination, and manual dexterity; along with the advantage of administering drugs continuously and in larger doses; besides the output of visible aerosol mist, giving more confidence to the patient. Drug substances commonly used for inhalation therapy in OAD, comprise bronchodilators and inhaled corticosteroids, besides some other drugs such as mucolytics. However, there are several issues related to nebulization therapy in OAD which need to be properly addressed such as indications of nebulizer use; choice of equipment; drugs, their dosages and combinations; adverse drug reactions etc., which have been discussed in this section.

Q 1. What are the indications for use of nebulization therapy in obstructive airway disease patients.?

Evidence statement:

- Nebulization therapy in obstructive airway diseases (OAD) is more useful in old age patients and in all other situations with cognitive impairment leading to poor hand breath coordination.
- Nebulization is also useful in acute conditions in OAD, requiring large doses of bronchodilators through continuous drug administration or through bolus therapy, to control the symptoms.

Recommendations:

- We recommend use of nebulization therapy in obstructive airway diseases (OAD) in patients unable to use handheld devices due to their altered physical or mental status; or have poor hand breath coordination. (III A)
- Nebulization therapy is also recommended in OAD with severe airflow limitation requiring high doses of bronchodilators for symptom control. (III A)

Q 2. Whether continuous or intermittent frequency of drug delivery should be used during nebulization in severe airflow obstruction?

Evidence statement:

- Continuous nebulization is more beneficial in patients with severe airflow obstruction and leads to decreased admission rate as compared to intermittent nebulization.

Recommendations:

- We recommend that preference should be given to continuous nebulization over intermittent in severe

airflow obstruction, however, in cases with less severe obstruction, either of the two can be used. [II A]

Q 3. What is the preferred driving gas for nebulization in patients of asthma and COPD?

Evidence statement:

- Using oxygen as driving gas for nebulization in hypoxemic asthma exacerbations is more beneficial.
- Using oxygen in hypercapnic COPD exacerbations leads to further CO_2 retention.
- For nebulization during transportation of COPD patients, air-driven nebulizers are to be used, however, in their absence, oxygen-driven nebulizer can be used for a maximum of 6 minutes. Use of battery-powered nebulizers are to be preferred in the ambulance services.

Recommendations:

- We recommend using oxygen as the preferred driving gas for nebulization in hypoxemic patients with asthma exacerbations. (II A)
- Air as the preferred driving gas for nebulization is recommended in hypercapnic patients with COPD exacerbations. (I A)
- Air-driven nebulizers are recommended to be used by the ambulance staff in the treatment of patients of COPD during transportation, however, in their absence, oxygen-driven nebulizer can be used, but for a maximum period of 6 minutes. In the same case setting, oxygen-driven nebulizer should be used in patients with acute asthma. (III A)
- It is recommended that ambulance services should be encouraged to use battery-powered nebulizers. (UPP)

Q 4. What are the drugs used for nebulization therapy in obstructive airway disease?

Evidence statement:·

- Various nebulized drugs used in obstructive airway diseases include corticosteroids, bronchodilators, and some other drugs.
- Inhaled corticosteroids in nebulized form include budesonide, fluticasone propionate, beclomethasone dipropionate and flunisolide.
- Inhaled nebulized bronchodilators include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (formoterol; arformoterol), SAMA (ipratropium bromide), and LAMA (glycopyrronium).
- Other drugs for nebulization in OAD include adrenaline, magnesium sulphate, ambroxol/N-Acetyl Cysteine and sodium cromolyn.

Recommendations:

- Bronchodilators in nebulized form are recommended to be used in obstructive airway diseases for the maintenance therapy or during exacerbations include beta-2 agonists: short acting (albuterol or salbutamol; levalbuterol or levo-salbutamol) and long acting (formoterol; arformoterol); and antimuscarinic agents: short acting (ipratropium bromide) and long acting (glycopyrronium) (UPP)
- Corticosteroids in nebulized forms recommended to be used in obstructive airway disease include budesonide, fluticasone propionate, beclomethasone dipropionate and flunisolide (UPP)
- Other nebulized drugs recommended to be used in non-responsive patients of obstructive airway diseases in certain special situations include adrenaline (epinephrine), magnesium sulphate, ambroxol/N-Acetyl cysteine, and sodium cromolyn. (UPP)

Q 5. What classes of *bronchodilator, inhaled corticosteroids* and their combination formulations are available for nebulization in obstructive airway disease?

Evidence statement:

- Single agent bronchodilators available in India for nebulization include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (arformoterol), SAMA (ipratropium bromide), and LAMA (glycopyrronium). Nebulized formoterol is not available in India.
- Single agent inhaled corticosteroids available in India for nebulization include budesonide and fluticasone propionate. Beclomethasone dipropionate and flunisolide are not available
- Combination bronchodilator formulations for nebulization available in India include SABA + SAMA (albuterol or salbutamol plus ipratropium; levalbuterol or levo-salbutamol plus ipratropium); and LABA + LAMA (Arformoterol + Glycopyrronium)
- Combination formulations of inhaled corticosteroids and bronchodilators available for nebulization in India include SABA + ICS (levalbuterol or levosalbutamol plus budesonide); and LABA + ICS (formoterol + budesonide)
- Other drugs available as single agents for nebulization in India include adrenaline (epinephrine), magnesium sulfate and ambroxol/N-acetyl-cystein. Sodium Cromolyn is not available now.

Recommendations:

- Bronchodilator drugs recommended to be used in obstructive airway disease, available in India in nebulized form as a single agent, include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (Arformoterol), SAMA (Ipratropium bromide), and LAMA (Glycopyrronium). Formoterol as a single agent in nebulized form is not available (UPP)
- Corticosteroids recommended to be used in obstructive airway disease, available in India in nebulized form as a single agent, include budesonide and fluticasone propionate (UPP)
- Bronchodilator drug combinations recommended to be used in obstructive airway disease, available in India in nebulized form, include SABA + SAMA (albuterol or salbutamol plus ipratropium; levalbuterol or levosalbutamol

plus ipratropium); and LABA + LAMA (Arformoterol + Glycopyrronium) (UPP)
- Combination formulations of inhaled corticosteroids and bronchodilators recommended to be used in obstructive airway disease, available in India in nebulized form, include SABA plus ICS (levalbuterol or levosalbutamol plus budesonide); and LABA + ICS (formoterol + budesonide) (UPP)
- Other drugs recommended to be used in obstructive airway disease for nebulization in certain special situations include adrenaline (epinephrine), magnesium sulfate and ambroxol/N-acetyl-cysteine. (UPP)

Q 6. How to select appropriate bronchodilators, single or in combination, in patients of asthma and COPD?

Bronchodilator use in cases of asthma and COPD has been dealt in this question under two separate heads:

Bronchodilators use in bronchial asthma:

Evidence statement:

- Nebulization with a combination of SABA and SAMA compared with SABA monotherapy has no extra benefit in asthma except in patients with severe airflow obstruction.
- Nebulized levalbuterol is more potent than albuterol and shows a similar bronchodilator response as compared to albuterol even when administered at one-half or one-fourth the dose.
- Arformoterol and formoterol in nebulized form have potent and rapid bronchodilator effects with the benefit of a prolonged duration of action. Arformoterol is a single enantiomer of formoterol and is more potent than it.
- LABA or SABA in combination with inhaled corticosteroids (Levalbuterol with Budesonide; Formoterol with Budesonide) in nebulized form can be used in cases of persistent asthma.
- All the nebulized SABA (albuterol and levalbuterol) with or without SAMA (Ipratropium bromide) and LABA (formoterol and arformoterol) available singly (arformoterol) or in combination with LAMA (Arformoterol with Glycopyrronium) or ICS (Formoterol with Budesonide) can be used as a rescue medication too during exacerbations in cases of asthma. (Formoterol in India is available only in combination with budesonide)
- Single dose nebulised formoterol fumarate (12 microg) was found to be equivalent to three doses of albuterol (3 doses of 0.15 mg/kg to a maximum of 2.5 mg. every 20 min. for one hour) in acute asthma in children. As needed formoterol and albuterol have similar safety profiles but compared with albuterol, formoterol reduced the risk of exacerbations, increased the time to first exacerbation and reduced the need for reliever medication.
- All the beta agonists carry a black box warning of the USFDA (United States Food & Drug Administration) and should not be used without controller medication (Inhaled corticosteroids) in the management of chronic persistent asthma due to risk of asthma related deaths.

Recommendations:

- Short acting inhaled beta-2 agonists (SABA) are recommended as bronchodilators of choice for nebulization in acute exacerbation of asthma. (I A)
- Combination therapy of short acting beta-2 agonists (SABA) plus short acting muscarinic antagonist (SAMA) via nebulization is recommended as a better option than SABA alone in moderate to severe exacerbation of asthma. (I A)
- Levalbuterol is recommended as a more potent bronchodilator than albuterol, producing the same bronchodilator effect in half the doses, however, it is more expensive (I A)
- Nebulized forms of formoterol and arformoterol are recommended as a maintenance therapy in asthma in combination with nebulized corticosteroids. These have a rapid onset of action and are potent bronchodilators too with a convenient BID dosage schedule. Nebulized SABA with inhaled corticosteroids can also be used for this purpose but has an inconvenient dosing schedule. (I A)
- Nebulized LABA are also recommended as a preferred rescue medication over albuterol during acute exacerbations of asthma as these are equally effective to it in a single dose with a prolonged effect as compared to multiple doses of albuterol (3 doses every 20 min. for one hour). (II A)
- Further, use of LABA also reduced the risk of exacerbations, increased the time to first exacerbation and reduced the need for reliever medication. (II A)
- It is recommended not to use beta agonists without controller medication in the management of chronic persistent asthma due to risk of asthma related deaths. (III A)

Bronchodilator use in chronic obstructive pulmonary disease (COPD):

Evidence statement:

- Nebulization with combination of short acting beta agonist (SABA) and short acting muscarinic antagonist (SAMA) is not superior to either of them used alone in acute exacerbation of COPD.
- Nebulized levalbuterol may have some advantages over albuterol but clinically significant differences between the two in terms of efficacy, occurrence of adverse effects, or hospital admissions is not seen. Nebulized albuterol is much cheaper also as compared to levalbuterol.
- Nebulized formoterol (LABA) is useful as bronchodilator for regular maintenance therapy in COPD and as-needed reliever therapy due to its rapid onset of action. However, it is only available in combination with budesonide in India and not as monotherapy.
- Nebulized formoterol has a prolonged duration of action and hence in COPD patients it is used in BID dosage and these patients show greater treatment satisfaction response when compared with short-acting bronchodilators delivered four times daily.

- Nebulized Arformoterol, another potent, selective, long-acting bronchodilator; acts in a way similar to formoterol but is more potent. It can also be used as a rescue medication and is safe too.
- Maintenance therapy in COPD with nebulized arformoterol or formoterol, both show a reduction in use of rescue albuterol use, but more so with arformoterol.
- Maintenance therapy with arformoterol reduces costly outcomes of COPD such as readmission rates, greater COPD severity, and fewer comorbidities than nebulized SABA users.
- Nebulized glycopyrronium bromide (LAMA), available as maintenance therapy in moderate to very severe COPD cases, shows a rapid onset of action with significant improvement in lung function and reduction in exacerbation rate and is safe too. It can also be combined with LABA and inhaled corticosteroids.
- Nebulized formoterol and Arformoterol (LABA), both have a synergistic effect in cases of COPD when used in combination with tiotropium bromide (LAMA), given as a dry powder inhaler. Now, nebulized glycopyrronium bromide has also been combined with these drugs safely with better efficacy and convenient BID dosage.
- The new combination of Arformoterol with glycopyrronium for nebulization makes its use more convenient with superior bronchodilator effect.

Recommendations:

- Nebulized SABA or SAMA, both are recommended in acute exacerbation of COPD and are equally effective. Their combination is not superior to either of them used alone. (I A)
- Nebulized levalbuterol has no definite clinically significant advantage over albuterol and both are also recommended to be used for rescue medication during exacerbation in COPD. Levalbuterol is more expensive than albuterol. (II B)
- Nebulized formoterol and arformoterol, both are recommended in long term maintenance use and as rescue medication during exacerbation in COPD cases. Both are potent bronchodilators and have the ease of administration having a BID dosage schedule. Arformoterol is relatively more potent. (II A)
- Nebulized Glycopyrronium, a safe new long acting antimuscarinic antagonist, is recommended as a maintenance therapy in moderate to very severe cases of COPD. It can also be combined with LABA and inhaled corticosteroids (I A)
- The new Arformoterol (LABA) with glycopyrronium (LAMA) combination in nebulized form, is recommended in cases of COPD as a more efficacious and convenient combination for the maintenance therapy. (II A)

Q 7. What are the dosages and side effects of nebulized bronchodilator drugs?

Evidence statements:

- Dose of albuterol is 2.5–5mg for each nebulization. The frequency of use is 2.5mg every 20 minutes for one hour and subsequently every 4-6 hours depending on the clinical response. For continuous nebulization albuterol is to be used at the dose of 5-10mg/hour for 3-4 hours depending on clinical response.
- Dose of levalbuterol is 0.63-1.25mg for each nebulization, half that of albuterol with a better/or equivalent bronchodilator effect.
- Dose of Ipratropium is 0.5mg for each nebulization. The frequency of use is 0.5mg every 20 minutes for 1 hour and subsequently every 4-6 hours depending on clinical response.
- Addition of intravenous albuterol to inhaled albuterol in acute severe asthma is of no added benefit.
- The Common adverse events with beta2-agonists are tremor, palpitations, dry mouth, headache, anxiety, and nervousness. Other less common ones are alteration in taste, tachycardia, dizziness, and hypokalaemia. Levalbuterol is relatively safe except for tachycardia and serum potassium level lowering effects.
- The common adverse events with anticholinergics are tremor, palpitations, dry mouth, and headache, while less common ones are alteration in taste, dizziness, anxiety, blurred vision and urinary retention.
- The dose of nebulized formoterol fumarate is 20 microg BID. It has been found to be safe for long term use. There are no changes in laboratory values including serum potassium and glucose; and treatment-related increases in cardiac arrhythmias, heart rate, or QTc prolongation.
- Nebulized arformoterol has been used in dosages from 30 to 50 microg in single or divided doses but 15 microg BID was found to be efficacious and safe. Its use is associated with a low incidence of cardiovascular side effects, having arrhythmia and ischemia similar to the placebo.
- Nebulized formoterol and arformoterol, both can be used during exacerbations in asthma and COPD in the same dosages due to their rapid onset of action. Both have a prolonged action up to 12 hours hence not requiring frequent dosages.
- Caution is required in cases of OAD with co-morbid conditions e.g. CVD and diabetes mellitus, while giving nebulized long acting beta2-agonists drugs, which may require periodical monitoring of blood glucose and cardiac parameters.
- Nebulized glycopyrronium has been used in dosages of 25 to 50 microg BID as a long-term maintenance therapy for moderate-to-very-severe COPD
- Nebulised glycopyrronium has been found to be safe and well tolerated with extremely low incidence of anticholinergic-related events and has been used safely even in the cases with cardio-vascular disease. Glaucoma-related adverse events are very rarely observed and urinary retention was not observed.

Recommendations:

- Recommended dosage of albuterol is 2.5 – 5 mg for each nebulization. In acute exacerbation of COPD and bronchial asthma, it is recommended in dosage of 2.5mg every 20 minutes for one hour and every 4-6 h subsequently depending on the clinical response. (I A)
- Recommended dosage of levalbuterol is 0.63-1.25mg for each nebulization, half that of albuterol. (I A)

- Recommended dosage of Ipratropium is 0.5mg for each nebulization. In acute exacerbation of COPD and bronchial asthma, nebulized ipratropium is given in dosage of 0.5mg every 20 minutes for one hour and every 4-6 hour subsequently depending on clinical response. (I A)
- The nebulized SABA and SAMA are well tolerated and safe with only few local or systemic side effects, more so with their combination therapy. Levalbuterol is relatively better tolerated than albuterol. However, caution is recommended in patients with morbid conditions e.g. cardiovascular diseases and diabetes etc. (I A)
- Recommended dosages of nebulized formoterol fumarate and arformoterol, for maintenance therapy in cases of asthma and COPD, are 20 microg BID and 15 microg BID respectively. (I A)
- Both, nebulized formoterol and arformoterol are safe on long term use with no serious adverse events including cardiovascular effects. However, it is recommended to have periodical monitoring of parameters in those having pre-existing CVD and diabetes mellitus, while using nebulized LABA. (I A)
- During acute exacerbations of asthma and COPD, use of formoterol or arformoterol in nebulized form is recommended in same dosages (I A)
- Recommended dosage of nebulized glycopyrronium (GBn), is 25 or 50 microg BID as a maintenance treatment for moderate-to-very-severe COPD (I A)
- Nebulised glycopyrronium (GBn) has been found to be safe and well tolerated with exceptionally low incidence of anticholinergic-related events and is recommended even in cases of COPD with cardio-vascular disease. (I A)

Q 8. What nebulized corticosteroids and their combinations (ICS + SABA/LABA/LAMA) are available in India?

Various forms of nebulized corticosteroids and their combinations available in India are given in Table 1.

Budesonide (O.5mg & 1.0mg per unit) and fluticasone (O.5mg & 2.0mg per unit) are available as single agents in two different strengths and budesonide is also available as dual combination with levalbuterol (Levo-salbutamol) in single strength (O.5mg + 1.25mg)) and with formoterol in two strengths (0.5 mg + 20 mcg per unit & 1.0 mg + 20 mcg per unit).

Q 9. What is the dosage, duration, frequency of use and side effects of treatment with nebulized corticosteroids in obstructive airway diseases?

Evidence statement:

- Nebulized corticosteroids are used as a therapeutic option in most cases of persistent asthma and during its exacerbations, especially among infants, young children, and elderly people
- Whereas budesonide (BUD) and fluticasone propionate (FP) are the two inhaled corticosteroids commonly available for nebulization, budesonide has been used more often in the studies with extensive data available, whereas fluticasone propionate has not so often been used.
- Fluticasone propionate in dry powder form in half the daily dose has been found to have better efficacy compared to BUD and BDP in cases of persistent asthma but concerns about local side effects have been reported.
- The dosage of nebulized BUD among infants and children (3 months-12 years) with asthma is 0.5 mg to 1 mg/day, going up to 2 mg/day, when starting treatment, during asthma exacerbation or during withdrawal of oral corticosteroid. Amongst adults and children (>12 years), the dose is 2 to 4 mg/day, though still higher doses may be necessary in very severe cases of asthma. Maintenance doses are typically 50% lower than the starting dose.
- Nebulized FP (1.0 mg) compared to BUD (2.0 mg) in BID dose in severe persistent asthma in adults is equally efficacious and safe. Among children (4-15 years) with mild asthma exacerbation, nebulized BUD (500 mcg) or nebulized FP (250 mcg), BID was found to be equipotent.
- The dosage of nebulized FP is half that of nebulized BUD i. e. 0.25 to 1mg BID in cases of persistent asthma and this can be increased up to 2.0mg BID in severe obstruction.
- Combining nebulized BUD or FP with bronchodilators show significant clinical efficacy compared to the placebo arm.
- Use of nebulized corticosteroids has also been correlated with reduction in relapses occurring in cases with persistent asthma compared with other asthma medications.
- Nebulized BUD and FP in children and adults with persistent asthma, have an oral corticosteroid-sparing effect, reducing the hospital stay, improve lung function, improve quality of life, and prevent acute exacerbations. (preventing visits to ED and hospital admissions)
- Nebulized corticosteroids have limited usefulness amongst cases of COPD, where it may be of some use during acute exacerbations or in cases having overlap of asthma (ACOS) with eosinophilic inflammatory disease of airways.
- Nebulized corticosteroids have been found to be equally effective as compared to oral/parenteral corticosteroids during acute exacerbations of COPD and are safer too, but further studies are needed.
- Nebulized BUD and FP, when used judiciously, are safe having exceedingly few systemic adverse effect common with systemic steroids (suppression of HPA axis, impaired growth in children, osteoporosis, fractures, glaucoma, cataracts, skin thinning etc.) and that too are dose related. These may only be associated with some local adverse effects (oral candidiasis, cough at time of inhalation, hoarse voice, and dysphonia).
- Risk of pneumonia in COPD or asthmatic patients is a threat to the ICS therapy which shows a dose-response relationship.

Recommendations:

- Nebulized corticosteroids, in the form of BUD or FP are recommended for use as maintenance therapy in the cases of persistent asthma, unable to use other inhalation devices, especially the infants, young children and elderly people. It improves their lung function, QOL; prevents acute exacerbations, visits to ED and hospital admissions and reduction in hospital stay; and reduces risk of relapses in these cases. (I A).
- The recommended dose of nebulized BUD for infants and children aged 3 months to 12 years with persistent asthma

is 0.25 mg to 0.5 mg BID going up to 1.0 mg BID during exacerbation. Starting dose in adults and children above 12 years is 1.0 to 2.0 mg BID, and still higher doses up to 4.0 mg BID can be given in very severe cases. The maintenance doses are 50% lower than the starting dose. Nebulized FP is more efficacious than nebulized BUD and is recommended in a dose ratio of 1:2 (I A)

- Nebulized BUD or FP in higher dosages have a promising role in the acute exacerbations of asthma or COPD, in place of systemic steroids, showing an oral corticosteroid-sparing effect, but their use is not recommended for want of fully evidence based studies. (I A)
- Nebulized BUD and FP are recommended to be combined with bronchodilators (LABA) for better efficacy in persistent asthma (I A)
- Nebulized FP and BUD are recommended for long term use and are safe too, if used judiciously, as no systemic adverse effects, commonly seen with the oral or parenteral corticosteroids, are seen. Only local side effects may be present. Risk of pneumonia in these cases remains to be a threat but it has a dose-response relationship (I A)

Q 10. What is the role of nebulized magnesium sulphate in management of obstructive airway diseases?

Evidence statement:

- Magnesium sulphate ($MgSO_4$) through intravenous route has been used in severe acute asthma as an additive to the usual bronchodilator therapy. It has been found to have a significant bronchodilator effect.
- Nebulized albuterol in comparison to nebulized magnesium sulphate has a better bronchodilator effect.
- The results with nebulized $MgSO_4$ as an additive to albuterol, when compared with albuterol alone in acute severe asthma, have been found to be variable, with some studies showing enhanced bronchodilator response while others showed no additional benefit of combination.
- Modest benefit in lung function and hospital admission has been seen when $MgSO_4$ was added to beta-2 agonist and ipratropium.
- Nebulized $MgSO_4$ is given as 3 to 4 doses of 100mg each, given every 20 min in addition to other drugs
- The adverse effects commonly associated with $MgSO_4$ nebulization include nausea, vomiting, thirst, flushing, drowsiness, confusion, muscle weakness, respiratory depression, loss of deep tendon reflexes, hypotension, and cardiac arrhythmias. These effects usually do not necessitate withdrawal of therapy.
- Bronchodilator effect as supplement to albuterol, shows modest benefit in lung function, and has impact on hospital admission. Its use was found to be safe

Recommendations:

- We recommend the use of nebulization with magnesium sulphate in 3 to 4 doses of 100 mg each in 3mL (3.3%), given every 20 minutes, as an add on to standard treatment in some refractory cases of acute severe asthma exacerbation. (I A)
- Nebulized magnesium sulphate in cases of severe asthma is recommended only to be used in combination with albuterol, or ipratropium and albuterol both, but not magnesium sulphate alone (I A)
- Nebulized magnesium sulphate is safe to be used in cases of severe asthma (I A)

Q 11. What special precautions are to be taken in elderly patients?

Evidence statement:

- The aging world's population is likely to be accompanied by an increasing number of older patients with asthma and COPD, many of whom may be the candidates for the use of nebulizers.
- Proper selection of aerosol delivery device between a nebulizer and MDI with spacer, among the elderly, needs to be done considering various factors related to the device and the patient
- Problems related to the use of nebulizer or MDI in this group of patients could be more, leading to their inappropriate use, which need to be identified and addressed to obtain the optimal benefit out of the medication used.
- Nebulization with mouthpiece as the interface is preferable over face masks in elderly to avoid exposure of the aerosol of nebulized drug on the eyes, preventing its adverse effects.
- The advancing age often is accompanied by a decline in response to beta-2 agonists, but not so much to ipratropium, hence, preference be given to combination of SABA with SAMA instead of increasing the dose of beta-2 agonists. Alternatively, SABA may be replaced by SAMA, keeping in view the toxicity to the SABA, especially in presence of co-morbidities in this group of patients. Formoterol and arformoterol use could be another safe option
- Eldery patients more often have comorbidities particularly ischaemic heart disease, glaucoma, prostatism etc. hence high dose beta 2 agonists need to be avoided.

Recommendations:

- Among the elderly in OAD patients, it is recommended to make an appropriate selection between nebulizer and MDI (with spacer), on merits considering various factors related to the device and the patient, to optimize treatment outcomes (UPP)
- Mouthpiece as an interface during nebulization amongst the elderly is recommended as the first choice over the face mask to avoid exposure of drug to the eyes to prevent ocular side effects. (II A)
- For the declining beta-2 agonists response in the elderly, combining use of SAMA to SABA or replacing SABA by SAMA is recommended instead of increasing the dose of SABA, keeping in view its toxicity, especially in presence of co-morbidities in this group of patients. (II A)
- Formoterol and arformoterol use in these patients is also recommended as another safe option (III A)
- Close monitoring for the adverse drug reactions in the elderly, while using nebulized bronchodilators, is

recommended, in view of high prevalence of the pre-existing co-morbid conditions in these patients (II A)

Section - III (Group - C): Nebulization therapy in the intensive care unit

Aerosol therapy is routinely administered in intensive care units (ICU) across the world, in both ventilated and non-ventilated patients, whether invasive or non-invasive. There are a number of drugs that are delivered as aerosols in the ICU and the list is gradually expanding. Bronchodilators and steroids are the most frequently used drugs followed by inhaled antibiotics. Metered dose inhaler is also often used besides the nebulizers. Among the nebulizers, jet nebulizer is the commonest to be used followed by ultrasonic nebulizers, and the vibrating mesh nebulizers. Nebulization in mechanically ventilated patients differs from that in spontaneously breathing patients, and its use is complex. The major difference between the two is that the administration of aerosols is usually dependent on the patient when they are spontaneously breathing while in mechanically ventilated patients it depends upon ventilator circuits, settings, device used, as well as the nurses administering it. Various factors that influence aerosol drug delivery to the lung in mechanically ventilated patients include selection of the device and its installation position in the nebulizer circuit, the humidification, temperature, gas density, patient position, endotracheal tube size, presence of airway obstruction, adjustment of the ventilator mode and parameters, drug formulation, its dose and frequency applied. Currently, there are no readily available guidelines which can be followed by ICU physicians and health care providers for delivery of aerosol therapy to the critically ill patients. This section describes various strategies for effective delivery of nebulized medications in mechanically ventilated patients.

Q 1. What are the indications for aerosol therapy in patients on mechanical ventilation (MV) ?

Evidence statement:

- Several drugs and substances have been used for nebulization in patients on mechanical ventilation.
- Common indications for nebulization in these cases include broncho-dilation, anti-inflammatory, anti-microbial, and mucolytic actions.
- Uncommon uses in these patients could be for use of vasoactive drugs, heliox, surfactants, humidification etc.

Recommendations:

- We recommend nebulization therapy commonly for broncho-dilation, anti-inflammatory, anti-microbial, and mucolytic purposes in mechanically ventilated patients (II A)
- Nebulization therapy is also recommended for some other purposes such as use of vasoactive drugs, heliox, surfactants etc in these patients. (IIA)

Q 2. What drugs are commonly administered through nebulization in intensive care unit patients?

Evidence statement:

- Commonly the drugs used for nebulization in the intensive care unit (ICU) can be for both, treatment of pathologies localized to the lungs as well as for systemic disorders.
- Several drugs have been used in nebulized form in the intensive care unit in mechanically ventilated patients or in animal models as summarized in Table 1.
- Bronchodilators are the most used drugs in the ICU to reduce the airway resistance and intrinsic PEEP.
- The role of bronchodilators in ICU in patients without OAD is uncertain as their usefulness has not been studied through RCTs. Moreover, these drugs have the potential to cause hypokalemia and cardiac arrhythmias; besides adding to the cost of treatment.
- The usage of inhaled antibiotics (mostly aminoglycosides and colistin) in treatment of ventilator-associated pneumonia (VAP), especially with resistant gram-negative organisms is developing mostly as an adjunctive therapy.

Recommendations:

- We recommend use of only those drugs from Table 1 for nebulization which are available commercially and are indicated in patients in an intensive care unit. (II A)
- Nebulized bronchodilators in ventilator-supported patients are recommended only in OAD and not in other diseases for want of RCTs to establish their beneficial effects and also considering issues of their toxicity and cost. (III B)
- Nebulized antibiotics are recommended only as adjunctive therapy in cases of ventilator-associated pneumonia (VAP) with resistant gram-negative organisms. (II A)

Q 3. What pre-procedure preparation should be done before administration of nebulization to mechanically ventilated patients?

Evidence statement:

- A good airway suction prior to nebulization is essential to ensure adequate ventilation and delivery of aerosol in mechanically ventilated patients since drug delivery is significantly reduced in presence of fluid and secretions in the ventilator circuit, endotracheal tube, as well as in patient's airways.
- Right angled elbow connectors; sudden changes in the diameter, narrowing and roughening of the inner surface of ventilator circuit components; connection between Y piece and endotracheal tube; and in-line suction catheters; reduce the nebulized drug delivery to the lungs.
- Routine use of mucolytic agents may increase the inspiratory airway resistance through their muco kinetic action.

Recommendations:

- Ventilatory circuits are recommended to avoid sharp angles, narrow and sudden changes in the diameter, and

need to be characterized by smooth curvatures and smooth inner surfaces. Use of in-line suction catheters should be avoided. (III A)
- Y-piece should be directly connected to the proximal tip of the endotracheal or tracheostomy tube. (UPP)
- It is recommended to have an effective suction of the ventilator circuit, endotracheal tube, as well as in patient's airways before nebulization to remove the fluids and secretions to have better ventilation and drug delivery. (III A)
- Mucolytic agents are not recommended for routine use to avoid inspiratory airway resistance due to increased secretions. (III A)

Q 4. Should the heated humidifier be switched off/Heat and Moisture Exchanger (HME) removed during aerosol therapy on MV?

Evidence statement:

- Some degree of humidification is always used during mechanical ventilation for the normal functioning of airway mucosa. Heated humidifiers have been shown to increase the droplet size and reduce drug deposition during nebulization.
- Heated humidifiers need to be turned off during the brief periods of nebulization (10-15 min), avoiding longer periods, however, usefulness of this practice is questionable as it takes up to 20 min. for heat and humidity to settle.
- Higher doses of the drug may be used if the heated humidifier is not switched off during nebulization to compensate for the loss, but these must be switched off for drugs which are costly and heat unstable (e.g. antibiotics).
- Heat and moisture exchanger (HME) hampers drug delivery, hence it must be removed during nebulization, except for the newer models with provision to bypass the filter in the HME during inspiratory gas flow.

Recommendations:

- Heated humidifiers are recommended to be switched off during nebulization for brief periods (10-15 min.), but longer periods need to be avoided. However, its usefulness has been disputed. (III A)
- It is recommended to use higher doses of drugs to compensate for the loss if heated humidifiers are not switched off, but for expensive and heat unstable drugs, it must be switched off to prevent drug loss. (III A)
- Heat and moisture exchanger (HME), which can hamper drug delivery, should be removed from the circuit during nebulization, except in newer models with provision to bypass the filter in HME during inspiratory flow. (III A)

Q 5. What type of nebulizer should be used for patients on mechanical ventilation?

Evidence statement:

- The efficiency of jet nebulizers for aerosol production is highly variable in their performance, even among different batches of the same brand, which raises concerns about the delivery of inhaled medications to critically ill patients.
- Jet nebulizers continue to be commonly employed in ventilator-supported patients since these are easy to use, and inexpensive compared with mesh and ultrasonic nebulizers, and because of the operator's familiarity with their use.
- The problem of additional flow of gas (6–8 L/min) from the compressor of the jet nebulizer into the ventilator circuit affecting the delivered volume and flow to the patient; besides having a longer treatment time and risk of circuit contamination; are its additional drawbacks.
- Jet nebulizers may inactivate or denature some of the drugs due to the shear forces and fall in the temperature of the reservoir fluid up to 15 degrees C during nebulization. This also can alter the drug concentration and the characteristics of the aerosol.
- The larger residual volumes after nebulization with the jet nebulizers result in lower aerosol delivery efficiency.
- The jet nebulizers continue to be commonly employed even though VMN has better drug delivery as compared to them.
- Ultrasonic nebulizers have the benefit of producing higher aerosol output, shorter nebulization time, and with no additional driving gas to the circuit affecting the ventilatory parameters. However, their cost, large size, and rise of solution temperature with the potential to denature some of the drug formulations make them undesirable for aerosol therapy in critical care.
- Vibrating mesh nebulizers (VMN) are more efficient than the jet or ultrasonic nebulizers, operate without adding gas to the circuit; with no change in temperature of drug solution; higher drug output with negligible residual volume. This increase in drug delivery requires dose adjustment to eliminate possible adverse effects due to overdosage.
- The VMN nebulizers are more expensive besides the fact that some of the suspensions or viscous drugs may clog the pores of the mesh affecting their performance.

Recommendations:

- Vibrating mesh nebulizers are recommended over the jet and ultrasonic nebulizers in mechanically ventilated patients due to their better efficiency, operation without adding extra gas to the circuit, and causing no change in temperature of the drug solution. Clogging of the pores of their mesh on using suspensions and viscous solutions is a problem faced with them. (III A)
- The additional flow of gas (6–8 L/min) from the compressor of the jet nebulizer into the ventilator circuit affects the delivered volume and flow to the patient which is not desirable. (III A)
- Denaturing the drug in the jet nebulizer, due to its sheer forces and due to lowering of temperature of drug solution by 15-degree C.; longer nebulization time; lower aerosol delivery efficiency and contamination of the circuit, are the other problems faced with it. (III A)
- Jet nebulizers, despite several disadvantages and their variable performance, continue to be used more frequently, due to operator's familiarity and ease of their operation, and for being less expensive. (III A)

- Pressurized metered-dose inhalers (pMDIs) continue to be recommended as an option for the drug aerosol delivery in mechanically ventilated patients as these have been shown to be equally effective to the nebulizers. (III A)

Q 6. Where should the nebulizer be attached in the ventilator circuit for maximizing aerosol delivery?

Evidence statement:

- The aerosol delivery is reduced in an artificial airway in patients who are tracheally intubated as compared to patients without artificial airways. However, with the advancing technologies this gap is getting reduced.
- Position of the nebulizer in the ventilator circuit can influence the efficiency of the aerosol delivery. However, some of the studies have also concluded that position had no effect on its efficacy.
- Placing a jet nebulizer between the endotracheal tube and the Y-piece has the least usefulness for the aerosol delivery. However, during clinical practice mostly it is placed in this position.
- Several in vitro studies on the lung models show that jet nebulizers have a better efficacy when placed at 15 cm from ventilator end.
- One of the RCT recently has shown that the optimal position of the nebulizer is 80 cm away from the Y-piece and that the aerosol delivery was lowest between Y-piece and the tracheal tube.
- The ultrasonic nebulizers and/or VMN on the lung models show a better efficacy at 15 cm from Y-piece in inspiratory limb, or at ventilator or humidifier (away from the Y-piece). Efficacy is less at the Y-piece. Variations in positions in between various experimental studies have also been found.
- Delivery of bronchodilators with the VMN is 2-4-fold greater compared with jet nebulizers placed at multiple positions in the artificial airways ($P < 0.05$). With an efficient nebulizer (VMN) the position of the nebulizer may not have much effect.

Recommendations:

- Position of a jet nebulizer at 80 cm away from the Y-piece is the recommended position for its optimal effect during mechanical ventilation (II A)
- Vibrating mesh nebulizer is recommended as the device of choice in these patients and it is to be connected at 10-15 cm from the Y-piece in the inspiratory limb. (III A)
- Much significance is not to be given to the position of nebulizer as it does not significantly affect the pulmonary bioavailability of bronchodilators, especially so with VMN. However, a position between the endotracheal tube and Y-piece is not recommended (UPP)

Q 7. What is the preferred position of a patient for aerosol therapy administration while on MV?

Evidence statement:

- Semi-recumbent position with head end elevated 20 to 30 degrees, for effective delivery of bronchodilators in patients on mechanical ventilation, has been found to be suitable. Antimicrobial agents can also be delivered in the same position.
- No studies comparing semi-recumbent positions with any other patient positions for aerosol delivery are available.
- International consensus statements also do not specify any specific position of patient.

Recommendations:

- Patients on mechanical ventilation, for the aerosol therapy, are recommended to be kept in semi-recumbent position with head end elevated to 20 to 30 degrees above horizontal position. (II A)

Q 8. What should be the ventilatory settings while administering nebulization?

Evidence statement:

- Small size of the endotracheal tube (ETT) in paediatric studies is associated with lower aerosol deposition but no significant difference has been shown in adult studies comparing sizes of 7 and 9 French.
- Aerosol deposition in patients with tracheostomy tubes has not been well studied and different studies show contradictory findings.
- Drug delivery is significantly greater in dry than humidified conditions inside the mechanical ventilation circuit.
- A longer duty cycle and inspiratory time are associated with significant increase in aerosol deposition.
- Volume-controlled ventilation was associated with significantly higher drug deposition as compared to pressure support mode (Higher deposition in proximal airways)
- The bias flow also has effect over aerosol deposition, increasing bias flow decreases the amount of aerosol deposition and this influence is more with jet nebulizer than VMN.
- Ventilatory settings for the optimal deposition of drug include, volume-controlled mode; higher tidal volumes of 500ml or more in an adult (Vt 8 ml/kg); lower inspiratory flow rate (30–50 L/min), higher inspiratory to expiratory time ratio (I:E ratio 1:1); longer duty cycle and inspiratory time; inspiratory pause for 20% of duty cycle; respiratory rate of 12 to 15 breaths per minute; lower bias flow; optimal positive end expiratory pressure (PEEP) of 5 to 10 cm H20; and short acting sedative administration to avoid asynchrony. These were associated with increased aerosol delivery in mechanically ventilated patients undergoing nebulization.
- Vibrating mesh nebulizers have been preferred to jet nebulizers due to better aerosol delivery.

Recommendations:

- There are no specific recommendations regarding the size of the endotracheal tube (ETT) in adult patients on mechanical ventilation undergoing nebulization and in those having tracheostomy tubes. (III A)
- It is recommended to have dry conditions in the mechanical ventilation circuit to have greater aerosol deposition in the airways. (II A)

- Following ventilatory settings are recommended in a mechanically ventilated patients undergoing nebulization: (II A)
  - Volume-controlled ventilation
  - Higher tidal volumes 500ml or more in an adult (Vt 8 ml/kg)
  - Lower inspiratory flow rate (30–50 L/min)
  - longer inspiratory time, and slower inspiratory flows improve aerosol delivery.
  - Higher inspiratory to expiratory time ratio (I:E ratio 1:1)
  - Longer duty cycle and inspiratory time
  - Inspiratory pause for 20% of duty cycle
  - Respiratory rate of 12 to 15 breaths per minute
  - Lower bias flow
  - Optimal positive end expiratory pressure (PEEP) of 5 to 10 cm H20
  - Short acting sedative administration to avoid asynchrony.
  - Use of vibrating mesh nebulizer is preferable.

Q 9. What is the place of Heliox (helium and oxygen mixture) in nebulized drug delivery to the lungs in mechanically ventilated patients?

Evidence statement:

- Heliox, a 70/30 mixture of helium and oxygen, is a low-density gas, which has been used in clinical practice for many decades in the treatment of upper and lower airway obstruction.
- Heliox may improve the aerosol deposition in the lungs during mechanical ventilation, but its use is technically complex, besides being expensive, and its usefulness in these patients has not yet been established.

Recommendations:

- Routine use of heliox in mechanically ventilated patients, though may improve nebulized drug deposition, is not recommended for being more expensive and technically complex to use. (II B)

Q 10. Should aerosol therapy during non-invasive ventilation (NIV) be administered via ventilator circuit while continuing NIV, or independently after discontinuing NIV?

Evidence statement:

- NIV is often used in patients with acute and chronic respiratory failure and many of these cases require aerosolized medications. Currently there is no commercially available system designed specifically for inhalation therapy during NIV.
- Majority of patients receive nebulization in between NIV sessions rather than via NIV circuit. However, short term cessation of NIV may not be possible in all patients.
- Combination of NIV along with nebulized aerosol therapy is more efficacious than aerosol therapy alone as seen on spirometry data among asthmatics. Improvements were also seen based on oxygen saturation, heart rate, respiratory rate, ICU and hospital stay durations, and reduction in the dose of bronchodilators.
- Position of the nebulizer at the mask or before Y limb of double limb circuit, or between exhalation port and the lung in single limb circuit has been found to be most effective for aerosol delivery.
- There is progressive increase in aerosol delivery with increase in inspiratory and expiratory pressures in the NIV; and a respiratory rate of 20 breaths/minute resulted in significantly higher deposition compared to 10 breaths/minute.
- Vibrating mesh nebulizers were found to be more effective than jet nebulizers in improving Borg scores, respiratory rate and forced vital capacity. In the healthy subjects, VMNs delivered 2-fold more radiolabeled drugs into the respiratory tract compared to jet nebulizers.
- Oro-nasal mask is the preferable interface in patients on NIV who require nebulization and in patients with massive sputum expectoration, nasal mask may be used as an option.

Recommendations:

- Aerosol therapy is recommended to be administered via the non-invasive ventilation (NIV) circuit and not directly by cessation of NIV in all the cases since the combination of the two is more efficacious. (III A)
- Alternatively, NIV may be disconnected for short duration for aerosol therapy on a case-by-case basis, depending on the clinical condition of the patient. (III A)
- Nebulizer should be positioned at the mask or before the Y piece of double limb circuit for optimal aerosol delivery. In the case of a single limb NIV circuit, a nebulizer should be attached between the exhalation port and the lung.(III A)
- Aerosol delivery increases progressively with increase in inspiratory and expiratory pressures and a respiratory rate of 20 breaths per minute is optimal for this purpose. (III A)
- Vibrating mesh nebulizers are recommended over the jet nebulizers for use during NIV and oro-nasal mask as the preferable interface. Nasal masks may be used as an alternative in those expectorating out large quantities of sputum. (III A)

Q 11. Should there be a pre-formulated checklist or methodology provided to nurses, respiratory therapists or physicians providing aerosol therapy during MV?

Evidence statement:

- There is no data available in favour or against the use of pre-formulated check lists for aerosol therapy among mechanically ventilated patients.
- Pre-formulated check list is likely to standardize the aerosol therapy for better drug delivery to the lungs and hence better treatment outcomes. Such a model check list is provided in Table 2

Recommendations:

- Use of pre-formulated check lists for aerosol therapy is recommended for mechanically ventilated patients and each hospital/ICU should develop a checklist for their own use. (UPP)
- A model pre-formulated checklist (Table 2) has been recommended which may be useful and can be modified according to the existing local conditions and requirements in a particular set up. (UPP)

Q 12. What infection control practices should be followed by persons administering aerosol therapy to mechanically ventilated patients?

Evidence statement:

- Aerosol devices come in contact with respiratory mucosa and their improper care may be associated with transmission of infection in mechanically ventilated patients.
- Nebulizers and its accessories are classified under the 'semi-critical' category and hence these require thorough cleaning and high level of disinfection. Few guidelines are available for the disinfection of these devices, however, manufacturer's instructions also need to be followed.

Recommendations:

- Aerosol delivery devices are categorized as semi-critical devices, which have the potential to transmit the infection, hence it is recommended to follow infection control measures properly among the mechanically ventilated patients in the intensive care unit. (UPP)
- Measures mentioned in table no. 3 for nebulization in the intensive care unit are recommended to be followed for proper conduction of the procedure and disinfection of the instrument. (UPP)

(Also see the instructions given in section I and V of these guidelines).

Section – IV (Group - D): Use of various drugs (other than bronchodilators and inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy

Aerosolized drugs have several benefits over other routes of drug administration, including a rapid onset of action, ability to achieve high concentrations in lungs with lower incidence of systemic adverse effects; and hence is often considered a preferred and convenient method of drug delivery. Nebulization, besides in obstructive airway disorders, is also being used for a variety of other clinical conditions, and is gaining popularity as an alternative mode of treatment for many difficult-to-treat conditions, both pulmonary and non-pulmonary. These other uses, as shown below, have been described in this chapter:

- Structural lung diseases: cystic fibrosis (CF) and non-CF bronchiectasis (Antimicrobial drugs; Mucolytic agents)
- Pulmonary arterial hypertension (PAH)
- Flexible bronchoscopy (Nebulized lignocaine)
- Upper airway obstruction (Croup)
- Lower respiratory tract infections (Hospital-acquired pneumonia-HAP, Ventilator-associated pneumonia-VAP, Non-CF bronchiectasis, Infective exacerbations of chronic respiratory diseases; Tuberculosis; NTM; Viral infections; Fungal infections)
- Palliative respiratory care
- Haemoptysis

Structural lung diseases: cystic fibrosis (CF) and non-CF bronchiectasis

Q 1. Should nebulized antibiotics be given in the long-term management of structural lung diseases?

Evidence statement:

- Inhaled antibiotics in cases of cystic fibrosis (CF) with infections of Pseudomonas aeruginosa (Pa), can prevent progression from a transient infection to a persistent or chronic infection and it can also lead to clinical improvement in patients having chronic Pa colonization. Evidence also exists regarding effectiveness of inhaled antibiotics, in terms of microbiological as well as clinical outcomes in these cases.
- Sufficient evidence is yet not available regarding antibiotic strategy for the eradication of early Pa infection in CF, however, inhaled anti-pseudomonas antibiotics probably may have a limited role. Many studies despite various flaws support the efficacy and tolerability of inhaled antibiotics in eradicating Pa from newly infected patients with CF and also for suppression of chronic persistent Pa colonization in these cases.
- There is probably no role of inhaled antibiotic therapy in the present time against chronic colonization and/or eradication of MRSA in CF.
- The role of nebulized antibiotics in patients of non-CF bronchiectasis is still evolving. These may help reduce the sputum bacterial load and reduce the risk of acute exacerbation in stable non-CF bronchiectasis and chronic bacterial infection.

Recommendations:

- Inhaled antibiotics in cases of cystic fibrosis are recommended to prevent progression of Pa from a transient infection to a persistent or chronic infection. It helps in both, microbiological as well as clinical outcomes in these cases. (IA)
- Inhaled antibiotics are also recommended, despite limitations, in eradicating early Pa infections in CF patients and inhaled anti-pseudomonas antibiotics are preferred for this purpose. (IA)
- While maintaining good standards in airway clearance, regular inhaled antibiotics should be administered for long term management of symptomatic chronic Pseudomonas infection in CF patients (IA)

- Inhaled antibiotics are not recommended for achieving early eradication or chronic suppression of MRSA infections in patients of cystic fibrosis (IIIA)
- Nebulized antibiotics may have a role in stable non-CF bronchiectasis and chronic bacterial infection in achieving early eradication, reducing bacterial load & decreasing frequency of exacerbations, but presently these are still not recommended for routine use. (IIA)
- Inhaled antibiotic therapy should not be used for prevention of airway colonization by bacteria in CF and non-CF Bronchiectasis patients (UPP)

Q 2. Should nebulized antibiotics be used for acute exacerbations in structural lung diseases?

Evidence statement:

- The most widely used antibiotic regimen for acute exacerbations in CF comprised at least two systemic antibiotics from different antimicrobial classes without additional inhaled antibiotics.
- Inhaled antibiotics have been explored either alone or in conjunction with oral antibiotics for milder exacerbations or with intravenous antibiotics for more severe infections.
- Available evidence on the use of inhaled antibiotics during acute exacerbations of CF due to Pa is still weak, trials themselves are not sufficiently powered, some showing effectiveness of inhaled antibiotics and others not favouring them.
- There is no evidence regarding use of nebulized antibiotics during acute exacerbations of CF due to organisms other than Pa.
- In non-CF bronchiectasis also the role of inhaled antibiotics (TNS or Amikacin), in addition to systemic antibiotics, in the management of acute exacerbations, sufficient evidence is not available and are contradictory too, however, it does lead to greater reduction in the sputum bacterial load and higher sputum bacterial eradication rate.

Recommendations:

- Inhaled antibiotic as an adjunct to systemic therapy (oral/parenteral) is yet not routinely recommended in acute exacerbations caused by Pseudomonas aeruginosa in cases of cystic fibrosis (CF). (II B)
- Use of inhaled antibiotics alone is not recommended in acute exacerbations in CF caused by organisms other than Pseudomonas aeruginosa (II B)
- Role of inhaled antibiotics in addition to systemic antibiotics is yet not established in acute exacerbations occurring in cases of non-CF bronchiectasis. (II B)

Q 3. Which antibiotics can be used for nebulization therapy in structural lung diseases?

Evidence statement:

- Various nebulized antibiotics used in structural lung diseases (CF and non-CF bronchiectasis) include Tobramycin, Amikacin, Gentamicin, Aztreonam, Colistin, Vancomycin, and Fluoroquinolones.
- Although nebulized antibiotics have been used for a long time, recent focus is more towards dry-powder formulations for simple, fast and convenient delivery; while having similar efficacy in CF patients. These dry powder formulations include tobramycin, ciprofloxacin, levofloxacin, liposomal amikacin, and colistin.
- There is insufficient evidence in favour of one inhaled antibiotic over the other in managing chronic infections and acute exacerbations in CF patients in terms of efficacy in reducing bacterial load, patient tolerability and safety profile; lung functions, exacerbations, quality of life, hospitalization rates, and adverse events.
- Inhaled Tobramycin remains the most efficacious and recommended antibiotic in early eradication and chronic suppression of Pseudomonas aeruginosa infection in patients with CF. Aztreonam lysine could be another alternative but it has the disadvantage of three times dosing
- Use of inhaled antibiotics in non CF bronchiectasis has been limited and is not yet established. Tobramycin has been used more widely, however, other antibiotics used include aztreonam, ciprofloxacin, gentamicin, and colistin
- The use of nebulized antibiotics was associated with increased risk of cough, dyspnoea, wheezing, dysphonia, and chest tightness, which were more with the use of nebulized Tobramycin.

Recommendations:

- Choice of inhaled antibiotic treatment for each individual patient should be based on efficacy of the drug, infecting organism, the available nebulization system, patient characteristics & physician choices as no antibiotic has proven to be superior to others (IA)
- Inhaled antibiotics are mainly recommended for use in CF patients for early eradication and chronic suppression of Pseudomonas aeruginosa infection.(IIA)
- Tobramycin in inhaled form in cases of CF with Pseudomonas aeruginosa infection is recommended over others due to its better efficacy, easy availability and cost-effectiveness. Other alternatives include Amikacin, Gentamicin, Aztreonam, Colistin, and Fluoroquinolones (IIA)
- Dry powder inhaled antibiotic formulations in these CF cases, in recent times, are preferred over nebulized forms, because of simple, fast and convenient delivery; with similar efficacy. (IIA)
- Inhaled antibiotics are yet not recommended for routine use in cases of non CF bronchiectasis, however tobramycin may be preferred over other antibiotics (aztreonam, ciprofloxacin, gentamicin, and colistin) (IIA)
- Carefulness needs to be observed for respiratory adverse effects of nebulized antibiotics such as cough, dyspnoea, wheezing, dysphonia, and chest tightness, more so with tobramycin (IIA)

Q 4. Should nebulized antibiotics be given as stand-alone therapy or as an adjunct to systemic antibiotics?

Evidence statement:

- Inhaled antibiotics of different classes with or without the use of oral/intravenous antibiotics, either as intermittent or continuous therapy have been commonly used for early eradication and chronic suppression of Pa in patients with CF. However, there is still insufficient evidence in favour of any particular strategy.
- However, their use as a stand-alone treatment during exacerbation in CF patients is not supported by the available evidence due to erratic drug absorption as well as poor tolerability.
- Role of nebulized antibiotics as a stand-alone therapy or with systemic antibiotics in non-CF bronchiectasis for chronic suppression of infection with its prolonged use or in acute exacerbation is still under study

Recommendations:

- Inhaled antibiotics can be used as standalone agents or in combination with systemic antibiotic therapy for early eradication and chronic suppression of Pseudomonas aeruginosa infection in CF patients, however, it lacks evidence as to which one of these two strategies is superior (IIB)
- Inhaled antibiotics are recommended only as add on therapy to systemic therapy whenever being used for acute exacerbations in CF (IIIA)
- Nebulized antibiotics, alone or in addition to systemic antibiotics, in non CF bronchiectasis, are still not recommended for routine use during acute exacerbation or for chronic suppression of infection. (IIA)

Q 5. Should nebulized mucolytics be used in the management of structural lung diseases?

Evidence statement:

- Altered rheological properties of mucus, its hyper secretion, and impaired clearance lead to decreased lung function, reduced quality of life and increased exacerbation rates in structural lung diseases.
- Cases of cystic fibrosis characteristically have mucus hypersecretion making them more vulnerable to infections and inflammation.
- Modest benefit has been shown with some of the inhaled mucolytic agents in CF patients in terms of reduced sputum burden and viscosity, improved muco-ciliary clearance, time to exacerbation, reduction in lung function decline, and improved quality of life. However, their role in non-CF bronchiectasis is yet not well established.
- Inhaled mucolytics seem to be a good adjunctive strategy in managing patients with structural lung diseases. Combination of inhaled mucolytics with antibiotics, though used as standard care, no data is available on this combination.
- Commonly used inhaled mucolytics include recombinant human-DNase, mannitol, normal and hypertonic saline.

Recommendations:

- Inhaled mucolytic therapy is recommended in patients with cystic fibrosis to improve the lung clearance index; prevent frequent exacerbations and lung function decline; and improve quality of life (IA)
- Presently, mucolytic therapy is not recommended in patients with non-cystic fibrosis bronchiectasis until more evidence accumulates. (IIIB)
- Mucolytics may be combined with inhaled antibiotics as part of standard care of these patients (UPP)

Q 6. Which mucolytics should be preferred in management of structural lung diseases?

<u>Cystic Fibrosis:</u>

Evidence statement:

- The available evidence supports the use of dornase alpha as mucolytic therapy in CF patients leading to improved lung function, decrease in incidence and severity of exacerbations, and improved quality of life, however, few adverse events may be seen.
- The use of mannitol in CF patients has been found to be efficacious in terms of improvement in lung functions and quality of life; and reduction in exacerbations, regardless of DNase use, however, side effects are more compared to DNase.
- Use of hypertonic saline (7%) has been shown to reduce pulmonary exacerbations and marginally improve the lung function and is well tolerated.
- Enough evidence for the use of nebulized N-acetyl-cysteine (NAC) as a mucolytic agent in CF patients is yet not available.

Recommendations:

- Dornase alpha is recommended as a preferred mucolytic therapy over other mucolytic agents in CF patients (IA)
- Mannitol may also be used alone or with dornase alfa in patients with CF (IIA)
- Hypertonic saline is also recommended as a good alternative for mucolytic therapy in CF patients and is preferred in a strength of seven percent (IIB)
- Nebulized N-acetyl cysteine (NAC) is yet not recommended as a mucolytic in CF (IIIA)

<u>Non-Cystic Fibrosis Bronchiectasis:</u>

Evidence statement:

- Inhaled DNase use in Non-CF bronchiectasis has shown either worsening in the form of more exacerbations or decline in lung functions or no beneficial effects. Mannitol use has also not shown encouraging results.

- Hypertonic saline (6 or 7%) has shown significant improvement in sputum viscosity, ease of expectoration, lung function, number of annualized antibiotic courses and emergency department visits in cases of Non-CF bronchiectasis. Hyaluronic acid with hypertonic saline has also been used with modest results in one study.

Recommendations:

- Hypertonic saline (6 or 7%) is recommended to be used as mucolytic in non-CF bronchiectasis (IIA)
- Dornase alpha and mannitol are not recommended to be used as mucolytic agents in non-CF bronchiectasis (IIA)

PULMONARY ARTERIAL HYPERTENSION (PAH)

Q 7. Is there an indication for nebulized drugs in management of PAH?

Evidence statement:

- There is a significant potential for use of inhaled medications in Pulmonary arterial hypertension (PAH) with several benefits. But there are limitations too to these inhaled drugs which restrict their current use.
- The benefits of inhaled drugs for PAH directly reaching the target organ include no systemic hypotension and reduction in ventilation perfusion mismatch leading to better gas exchange, low dose requirement and thus a lower cost. However, these have the limitations of increased dose frequency besides erratic drug delivery to the lungs and respiratory adverse effects.

Recommendation:

- Inhaled drugs have a great potential with several benefits in the management of PAH. However, these have limited usefulness in the present time (IIB)

Q 8. Which class of inhaled drugs is indicated in pulmonary arterial hypertension (PAH) and in which group of patients?

Evidence statement:

- Main classes of drugs for use in PAH via the inhaled route include nitric oxide (NO) and the prostacyclin analogues and all the remaining drugs are experimental only.
- The use of nitric oxide is for pulmonary hypertensive crisis only and it is still under investigation for treating chronic pulmonary hypertension.
- Commonly used agents through inhaled route are prostacyclin analogues which include - epoprostenol, iloprost and treprostinil, which are indicated in advanced PAH (WHO functional class III and IV).
- Epoprostenol has a noticeably short half-life (2–3 minutes) and needs to be given by continuous nebulization making it suitable only for acute pulmonary hypertension crises in critically ill patients and patients on MV and not for treating patients of chronic PAH in an outpatients setting.
- Iloprost has a half-life of 7 – 8 minutes and a pharmacodynamic half-life of thirty minutes requiring a cumbersome dosing of 6 – 9 times per day. It is usually prescribed for out-patients with moderate-to-severe PAH who have declined for infusion therapy. It is given by proprietary inhalation device and the starting dose is 2.5 μg per inhalation, which can be up titrated to 5 μg if required
- Inhaled iloprost has also been used with bosentan but with variable results
- Treprostinil has the longest half-life of 3 – 4 hours requiring less frequent dosing but is available only as a proprietary inhalational device incorporating ultrasonic nebulizer which is not to be used in MV patients Its use through jet and VMN has so far not been standardized either in MV or in spontaneous breathing patients.
- The usual recommended dose of treprostinil is 54 – 72 μg per inhalation 4 times a day which has shown clinical benefits in various studies.The patients on parenteral therapy can also be shifted to inhaled therapy and conversely.

Recommendations:

- Nebulized prostacyclin analogues (treprostinil and iloprost) are commonly recommended in the treatment of advanced pulmonary arterial hypertension (WHO-FC-III and FC IV). (UPP)
- Epoprostenol, another prostacyclin analogues, with a half life of 2-3 minutes, is only recommended for continuous nebulization in acute pulmonary hypertension crises in critically ill patients and those on mechanical ventilation, where it has compared favorably to nitric oxide. (II B)
- Nebulized Iloprost or Treprostinil, either of the two may be used, however, treprostinil may be preferred because of its longer half-life (II B)
- Iloprost and treprostinil are currently only used as a proprietary inhalational system and their use with regular nebulizers is not yet well standardized and hence is not recommended. (II B)
- Nitric oxide is recommended to be used for pulmonary hypertesive crisis only (UPP)

Q 9. Are nebulized drugs to be given as stand-alone therapy or as adjunct to other oral drugs in PAH?

Evidence statement:

- The choice of therapy for PAH depends upon several factors such as the demonstration of vaso-reactivity, functional status, availability of agents, risk category, etc
- Nebulized drugs are best used as add-on agents in patients not controlled on one or two oral drugs, and their severity is not to such an extent to warrant infusion therapy.
- Nebulized therapies are not the choice for initial treatment of PAH for their limited efficacy and high cost and are also not the substitutes for infusion therapy in unstable patients since these cannot deliver high doses.
- Inhaled prostacyclin such as iloprost and treprostinil are used less often in the PAH population compared with the oral or infused medications.

Recommendations:

- Nebulized drugs are only recommended as an add on therapy to those who have failed to attain improvement goals with one or two oral drugs but are not the candidate for infusion therapy. (IIA)
- Nebulized drugs are not recommended for initial treatment of PAH and also not as a substitute for infusion therapy in unstable patients.(IIA)

FLEXIBLE BRONCHOSCOPY

Q 10. Is there a role of using nebulized lignocaine during flexible bronchoscopy?

Evidence statement:

- Nebulization with lignocaine does not offer any benefit in flexible bronchoscopy over other methods and the amount of drug delivered is also more.
- 'Spray-as-you-go' is a better technique providing adequate and selective local anaesthesia to the airways and prevents overdose of lignocaine.

Recommendations:

- Routine use of nebulized lignocaine in patients undergoing flexible bronchoscopy under conscious sedation is not recommended. (IIA)
- It is recommended to use 'spray-as-you-go' technique for the local anaesthesia to the airways during flexible bronchoscopy. (IIA)

UPPER AIRWAY OBSTRUCTION

Q 11. What are the indications of using nebulized drugs for management of upper airway obstruction due to Croup?

Evidence statement:

- Nebulized drugs in the form of glucocorticoids or epinephrine are useful in most cases of upper airway obstruction due moderate to severe croup as an alternative to the systemic therapy.
- Nebulized epinephrine leads to a significantly smaller croup score after 30 minutes of its administration.

Recommendations:

- Nebulized drugs belonging to the group of glucocorticoids or epinephrine are recommended to be used in the management of upper airway obstruction due to croup in moderate to severe cases as an alternative to systemic therapy (II A)

Q 12. Which nebulized drugs should be used in management of Croup?

Evidence statement:

- Glucocorticoids in systemic (oral or parenteral) or in nebulized form and nebulized L-epinephrine are used in upper airway obstruction due to croup in moderate to severe cases. A single-dose oral glucocorticoids treatment is enough for cases of mild croup.
- Among glucocorticoids, dexamethasone orally or intramuscularly (0.15–0.6 mg/kg); or oral prednisolone (1–2 mg/kg); or nebulized budesonide (1-2 mg); or alternatively nebulized L-epinephrine in doses of (0.5 ml/kg of 1:1000 solution) can be used.
- Nebulized budesonide and L-epinephrine are equally effective, however, a combination of the two is preferred for improved efficacy since L-epinephrine has an early action and as it decreases steroids begin to work.
- Normally L-epinephrine is preferred to racemic epinephrine for being safe, cheap and easily available. Systemic steroids are also preferred over nebulized ones

Recommendations:

- Systemic steroids (oral or parenteral) are preferred over nebulized ones in acute upper airway obstruction due to croup (IIA)
- Nebulized epinephrine is recommended in cases of moderate to severe croup and L-epinephrine should be preferred over racemic epinephrine (IIA)
- Nebulized epinephrine and nebulized budesonide both are equally effective but a combination of the two is recommended while managing patients of croup (IIB)

LOWER RESPIRATORY TRACT INFECTIONS

Q 13. *Should nebulized antibiotics be used in management of acute bacterial lower respiratory tract infections (LRTIs)?*

Evidence statement:

- The antibiotics that can be administered by nebulization include Ceftazidime, Colistin, Aminoglycosides (Tobramycin, Amikacin, Gentamicin); Fluoroquinolones (Levofloxacin), Aztreonam etc.
- Nebulized antibiotics have consistently demonstrated intrapulmonary concentrations several folds higher than those achieved after parenteral administration, thus having a great potential for use against multi drug resistant (MDR) gram-negative pathogens.
- Liposomal encapsulation of aminoglycosides can further prolong the residence time and increase concentrations within the lungs, minimizing systemic absorption.
- However, there is not enough evidence in support or against the use of nebulized antibiotics for acute bacterial lower respiratory tract infections including acute pneumonia, lung abscess, etc.
- To bring inhaled antimicrobials into clinical use in patients with acute LRTIs, further studies assessing the efficacy and safety of these agents is needed.

Recommendations:

Nebulized antibiotics, in absence of high-quality efficacy data, are not yet recommended for management of patients with acute bacterial lower respiratory tract infections, acute pneumonia, and lung abscess. (IIIA)

Q 14. Should nebulized anti-tubercular drugs be used in management of tuberculosis and non-tuberculous Mycobacterial infections (NTM) of lungs?

Evidence statement:

- Inhalation therapy has great potential for the treatment of lung diseases due to Mycobacterium tuberculosis (MTB) and Non-Tuberculous Mycobacterial (NTM) infections having several inherent benefits over systemic therapy.
- Nebulized amikacin, both non-liposomal and liposomal forms, as an add on therapy, has been found to be effective and relatively safe for NTM lung diseases, including some intractable infections. Nebulized liposomal amikacin has limited systemic toxicity and is safe also compared to non-liposomal amikacin. However, further RCTs are required to evaluate the benefit:risk ratio.
- Nebulized amikacin should be considered in place of intravenous amikacin when systemic administration is impractical, contraindicated, or where long-term treatment is required.
- Nebulized amikacin, in patients of CF having NTM infection, can be combined during the continuation phase of oral macrolides, with 2–3 additional antibiotics (minocycline, clofazimine, moxifloxacin, linezolid)
- High concentrations (much higher than the MIC) of ATDs (isoniazid, rifampicin, and pyrazinamide) have been detected in the epithelial lining fluid (ELF) and alveolar macrophages (AM) in healthy human volunteers after inhalation of low dose of these drugs as compared to levels attained after standard oral dose and with negligible serum levels.
- Not enough work has been done on inhaled ATDs against MTB, in spite of its great potential, both against sensitive and resistant strains and it remains to be an active area of research. Respirable insoluble micro and nanoparticles of ATDs are also under development but are limited to animal studies.

Recommendations:

- Nebulized Amikacin is recommended in the management of difficult to treat NTM lung disease in combination with standard multidrug therapy. Liposomal forms of amikacin are preferred over non-liposomal forms for safety reasons (II B)
- Inhaled amikacin along with 2–3 additional antibiotics (minocycline, clofazimine, moxifloxacin, linezolid) has been recommended during the continuation phase of oral macrolides in cases of cystic fibrosis developing NTM infection. (I B)
- Nebulized anti-tubercular drugs are not yet to be used for the management of pulmonary tuberculosis, however, their great potential needs to be studied by further research. (UPP)

Q 15. Should nebulized antiviral drugs be used in management of Viral Lower Respiratory Tract Infections (LRTI)?

Evidence statement:

- Antiviral drugs through inhaled routes may be useful in treatment of influenza, as it limits their systemic toxicity, and enough concentration can be reached by aerosolization. However, these are still not used widely.
- Aerosolized ribavirin is used in treating respiratory syncytial virus (RSV) infection of lower respiratory tract especially among infants and children, showing faster resolution of illness. However, it is important to avoid drug exposure to pregnant HCWs because of its teratogenic effects.
- Zanamivir only available in dry powder form, is efficacious in treatment of influenza, initiating therapy for maximum benefit within 48 hours of symptom onset, and has been found to be more effective than oral oseltamivir. Its nebulized form is not approved due to fatal adverse effects.
- Laninamivir is a long-acting version of Zanamivir, used in inhaled form as dry powder inhaler, for the treatment and prophylaxis of influenza A and B virus infections in both adults and children as a single dose regimen due to its long persistence in the lung. However, the drug still awaits worldwide approval and presently it is not available for nebulization.
- Use of inhaled antiviral drugs should be individualized on a case-to-case basis depending on drug availability, patients' clinical status and immune competence, cost-effectiveness, etc.

Recommendations:

- Nebulized ribavirin is recommended in treatment of respiratory syncytial virus infection of lower respiratory tract especially among infants and children. However, precautions need to be taken to prevent exposure to pregnant healthcare workers due to its teratogenic effects. (IIA)
- Currently use of inhaled Zanamivir, available as dry powder diskhaler, is recommended in treatment of patients with influenza, initiating therapy during the first 48 hours of onset of symptoms. It is more effective than oral oseltamivir, however, its use in nebulized form is not recommended. (IIB)
- Laninamivir, a long-acting version of Zanamivir, available only as inhaled dry powder (diskhaler), is recommended in influenza A and B virus infections, both for treatment and prophylaxis among adults and children. It is yet not available for nebulization therapy. (IIIB)

Q 16. Should nebulized antifungal drugs be used in management of fungal infections of lower respiratory tract (LRT)?

Evidence statement:

- Nebulized antifungal drugs have been used for the prophylaxis and treatment of respiratory infections due to

fungus which are commonly seen in organ transplant patients and those with immunodeficiency states.
- Nebulized pentamidine has been used in the treatment and prophylaxis of Pneumocystis jirovecii pneumonia, a life-threatening infection, in immunocompromised and organ transplant patients, especially where first line drugs like trimethoprim-sulfamethoxazole cannot be used or are contraindicated.
- Nebulized formulations of Amphotericin-B, have been used as an adjunctive therapy to systemic antifungal drugs for the prophylaxis and treatment of of pulmonary aspergillosis infections, including those difficult-to-treat, in settings of immunosuppressive states and transplant patients. Its intravenous administration to achieve desired lung tissue doses is limited by the toxicity.
- Amphotericin B is available in two forms, deoxycholate or liposomal, and both forms were found to be safe and well tolerated.
- Long-term prophylaxis with Liposomal Amphotericin B has been found to be useful and safe for preventing aspergillus infection in lung transplant patients.
- Nebulized liposomal amphotericin B in combination with IFN-γ and GM-CSF has also been successfully tried for the treatment of post-influenza pseudomembranous necrotizing bronchial aspergillosis infection.

Recommendations:

- Nebulized antifungal agents for the prophylaxis and treatment of respiratory infections due to fungal diseases are recommended to be used in the immunodeficient and organ transplant patients. (II B)
- Nebulized Pentamidine is recommended in these patients in the prophylaxis of Pneumocystis jirovecii pneumonia especially as an alternative to first line drugs. (II B)
- Nebulized amphotericin B, in deoxycholate or liposomal form, is recommended in prevention and treatment (as an adjunctive therapy); of invasive Aspergillus pneumonia in immuno-compromised and lung transplant patients with preference to its liposomal form (II B)
- Nebulized liposomal amphotericin B in combination with IFN-γ and GM-CSF also has a potential to be used in post-influenza pseudo-membranous necrotizing bronchial aspergillosis infection which needs further studies. (III B)

PALLIATIVE RESPIRATORY CARE

Q 17. Is there any role of nebulized drugs in palliative respiratory care for patients?

Evidence statement:

- Nebulized drugs have a potential role in patients with terminal respiratory illnesses, particularly with problems like dyspnoea and cough, that are difficult to palliate.
- Various nebulized drugs that can be used for palliation in the diseases like COPD, lung cancer, ILD, PH etc; include opioids, furosemide, local anaesthetics, mucolytics, bronchodilators, steroids etc; however, more research is needed to assess their efficacy, combination with other drugs, and safety. The results in published studies are mostly objective and not validated

Recommendations:

- Nebulized drugs are recommended to be used in palliative respiratory care in terminally ill patients. (III B)
- The drugs mostly used include opioids, furosemide, local anaesthetics, mucolytics, bronchodilators, steroids etc, for diseases such as malignancies, advanced lung diseases and others (IIIB)

Q 18. Which nebulized drugs can be used as part of palliative respiratory care?

Evidence statement:

- Low dose oral opioids can improve breathlessness in end-stage disease like malignancy or COPD, but concerns about adverse effects like constipation, sedation, and respiratory depression, limit their use.
- The role of nebulized opioids for use in palliation of chronic dyspnoea during the end-of-life period is not yet established, however, there are no treatment related adverse events seen with it. Until larger long-term controlled studies are completed, their use to treat dyspnoea should be assessed on a case-by-case basis. Commonly used nebulized opioids include morphine, hydromorphone, and fentanyl.
- Nebulized furosemide for palliation of dyspnoea could be another option, however, current available evidence is unable to draw out conclusions.
- Nebulized local anaesthetics can relieve intractable unproductive cough in terminal malignant and non-malignant diseases for which no other treatment has been found effective. Nebulized lignocaine and bupivacaine have been used during the end-of-life period for this purpose. However, enough evidence is not available and more controlled studies are required to generate data to find out its usefulness.

Recommendations:

- Nebulized opioids may be recommended for palliative therapy of chronic dyspnoea in advanced diseases such as COPD and malignancy and other respiratory diseases during their terminal phase (II B)
- Nebulized furosemide could be an option but is not yet recommended for palliation of chronic dyspnoea in advanced/terminal diseases (III B)
- Use of nebulized lignocaine or bupivacaine is recommended for palliation of chronic cough common in terminal malignant and non-malignant diseases. (III B)

Q 19. What is the role of nebulized tranexamic acid in controlling haemoptysis?

Evidence statement:

- Many patients with lung diseases suffer from the frequent significant submassive hemoptysis, resulting in hospital stays, poor quality of life, and sometimes even invasive procedures
- Nebulized tranexamic acid (TXA), an anti-fibrinolytic agent, seems to be a safe, effective, and noninvasive method for controlling non-massive haemoptysis in select patients or as a palliative therapy.
- Nebulized TXA in doses of 500 mg thrice a day led to resolution of haemoptysis within 2 - 5 days, shorter mean hospital stay and lesser number of patients requiring invasive procedures such as interventional bronchoscopy or angiographic embolization to control the bleeding.
- Nebulized tranexamic acid, is a safe, effective, and non-invasive method for controlling non-massive haemoptysis in select patients and may be useful as a palliative therapy.

Recommendations:

- Nebulized Tranexamic acid, in a dose of 500 mg thrice daily, is recommended for control of bleeding in lung disease of varied etiology having non-massive haemoptysis. (II B)
- Nebulized Tranexamic acid helps control haemoptysis leading to shorter hospital stay and reduced requirement of interventions to control bleeding, besides being safe. (II B)

Use of nebulization as an alternative method of drug delivery is a rapidly growing area of patient care. Currently popular nebulized medications like bronchodilators and steroids provide rapid symptomatic relief in many life-threatening clinical situations. Recent research has focused on various drugs other than bronchodilators and steroids, which may provide benefits to many patients who otherwise cannot be treated or would be at a risk of systemic adverse effects of the drugs. More research and practical experience are likely to bring many of the previously known drugs for various clinical conditions to desirable efficacious levels in nebulized form (Table 3). However, despite the potential benefits, nebulization therapy with these drugs has its own share of adverse drug reactions which should be kept in mind while using them (summarized in Table 4).

Section – V (Group - E): Domiciliary/Home/ Maintenance nebulization therapy; public and healthcare workers education./

Nebulizers are a useful alternative to handheld inhalers, especially in advance age group, critically ill patients, infants, and children, since optimum drug delivery with nebulizer is not completely dependent on patient effort as with handheld devices, and it can also be useful in various settings such as at home, in hospital, in an emergency room, and in a long-term care. Their use in the present time is not only restricted to the obstructive airway diseases (OADs), but has gone much beyond, and several other new indications and drugs are being added to the nebulization therapy. During the recent past, there have also been several advances in nebulizer technology, making them more patient friendly besides being more efficacious. Presently, patients with chronic OADs and often some other diseases, may require long-term use of nebulized drugs at home, including bronchodilators, anti-inflammatory, and other drugs. Various names have been used for this form of nebulization such as home or domiciliary or maintenance nebulization, however, in this section of guidelines, we shall be using 'Home nebulization' or 'Domiciliary nebulization' both the terms interchangeably.

Domiciliary nebulization, today, is an effective way of delivering aerosol therapy at home for the convenience of the patient, during specific situations, for a range of respiratory conditions, however, this must be properly and judiciously used to achieve the desired targets without harming the patient.

One of the important benefits of the home nebulization could be an early discharge of some of the patients from the hospital making their stay shorter, and, in some cases may even be instrumental in avoiding admission to a hospital by offering relief and sometimes during need it can also deliver bronchodilators in high doses during exacerbations. However, while planning nebulization therapy, it is also equally important to identify a specific nebulizer type for a patient for his requirements and to ensure its optimal use. Many of the aspects of home nebulization have been covered in this section.

Q 1. What is the aim of domiciliary/home/maintenance nebulization?

Evidence statement:

- Home nebulization should be used in a selected set of patients who are unable to use other modes of inhaled drug therapy and who need it for prolonged periods on a regular or frequent basis.
- It has been observed that 28 to 68% of patients do not use handheld devices properly; and 39 to 67% of HCW are unable to demonstrate correctly the critical steps for their proper use. All attempts must be made to ensure a correct technique to use the handheld devices properly before switching over the patients to nebulizer therapy.
- Proper selection of an inhalation device for an individual is critical to deliver a drug to the lungs safely and effectively to get the desired results.
- Nebulizer therapy does not require the person to coordinate their breathing with the machine as with the MDI, nor it requires a high inspiratory capacity as with DPI, which makes it easier to use a nebulizer than the hand held inhalation devices.

- The term domiciliary/home/maintenance nebulization is specifically used where the duration of nebulization therapy is of more than or equal to 2 weeks.

Recommendations:

- Domiciliary/home/or maintenance nebulization is recommended to safely and effectively deliver a therapeutic dose of the required drug, in a selected set of patients, who are not able to use other modes of inhaled drug therapy and need it for regular or frequent use for prolonged periods. (UPP).
- The handheld devices (MDI and DPI) have their own shortcomings especially in case of infants and elderly and nebulization therapy is recommended to overcome these problems. (III A).
- It is recommended to make all attempts to ensure a correct technique for patients to use the handheld devices properly before switching over to a nebulizer for the safe delivery of medication. (UPP)
- Patients requiring nebulization for two weeks or more are categorized under domiciliary home, or maintenance nebulization; the different terminologies used for this form of inhalation therapy. It is recommended for a variety of medical conditions and is used to deliver many types of medicines (UPP).

Q 2. What are the indications of domiciliary/home/maintenance nebulization therapy?

Evidence statement:

- Selection of patients for domiciliary/home/maintenance nebulization must be done properly based on several factors and indications.
- The indications to decide domiciliary nebulization in a case are based on the type of disease; patients' characteristics; and drug/drugs prescribed. Patients must properly be evaluated and assessed for the need of home nebulization therapy based on these factors.

Recommendations:

- It is recommended that the selection of domiciliary/home/maintenance nebulization is done properly based on the indications and not just arbitrarily. (UPP)
- The criteria recommended for the selection of domiciliary/home nebulization must be based on one or more of the following factors: type of disease; patient's characteristics; and drug/drugs to be nebulized. (More details in the text) (UPP).
- Several diseases and conditions demand a prolonged or frequent use of nebulization and conditions requiring high dosages that cannot be given through handheld devices (UPP).
- The selection must also consider the physical, mental, and physiological characteristics of the patient and his previous experience with an inhalation device. (UPP)
- Domiciliary nebulization criteria should also include the type of drug (drug available only in liquid form), long term maintenance treatment (Bronchodilators and corticosteroids), use as an adjunct therapy for prophylactic or therapeutic use (Antibiotics). (UPP)

Q 3. What are the issues with nebulization during travel?

Evidence statement:

- Medical equipment is permitted in various travel modes as per regulations in different countries. Most of the airlines allow medical equipment which are battery operated. In India, no specific restrictions are cited. Policies in the air travel may be variable with different airlines which need to be checked for nebulizers and nebulizer fluid before the travel.
- U.S. Transportation Security Administration permits to carry Nebulizers, C-PAPs, BiPAPs and A-PAPs, both in the 'Carry on bags' and 'Checked bags'. However, it is always preferable to check regulations in the country/countries of travel.
- Nebulizer and the fluid are preferably carried in the 'Carry on bags' to be available for use during need. In-flight use of nebulizer and oxygen may require prior permission/intimation.
- Nebulization fluids, during the flight, are exempt from the 3-1-1 liquids rule and are permitted in reasonable quantities, in excess of the normal permissible limit of 3.4 ounces quantities.
- Different countries have different power points and voltages hence always carry a voltage converter, plug adapter, a car socket adapter, and also additional batteries etc during any trip.
- Battery powered portable nebulizers are preferable during the travel but their performance may be variable depending on type of nebulizer requiring dose and other adjustments.
- No regulations could be cited for in country travel by car or rail

Recommendations:

- Nebulizers usually are permitted during the air travel, both in-country and international travel, however, prior intimation/permission is preferable, especially if it is to be used during the flight inside the cabin. It is also preferable to carry the nebulizer in 'Carry on bags'(UPP)
- Enquire details and regulations for the use of concomitant oxygen therapy (as per physician's recommendation), and check regulations on liquid packs of nebulization fluid, though these are exempt from 3-1-1 liquids rule and one may carry in excess of 3.4 ounces in reasonable quantities. (UPP)
- Battery operated equipment, preferably a new generation portable handheld nebulizer should be taken during any travel and one must also carry extra batteries and all accessories to charge and run the equipment. (UPP)
- For the change over to a portable nebulizer it is recommended to consult a physician about the type of equipment, instructions on its usage and modifications in drug dosages if any. (UPP)

- There are no regulations available in the country over the use of nebulizer during road and rail travel. (UPP)

Q 4. What are the patient's limitations to use nebulizer at home?

Evidence statement:

- Nebulizer use has always attracted less attention and has not been as well studied as pMDI and DPI.
- Several limitations may be encountered by patients during the home nebulization therapy that may be linked to sub-optimal outcomes. These are more commonly seen among the elderly COPD patients.
- Comorbidities, such as diabetes and cardio-vascular diseases, need to be watched carefully and monitored for their laboratory and cardiac parameters.
- Various limitations encountered include dependency on caregivers, impaired coordination, physical limitations, mentally challenged, and severely impaired cognitive status.
- Proper instructions and education on home nebulization and proper monitoring of cases directly or through a self management plan must always be done properly by the physician.
- The duration of the nebulization therapy is to be decided by the physician

Recommendations:

- Dependency on the caregivers is a major limitation during home nebulization amongst elderly and paediatric population. Other limitations include physical disability, mentally challenged, severely impaired cognition, and impaired visual acuity. These need to be identified and addressed by the physician to avoid sub-optimal therapy (III B).
- Proper initial instructions and education of patients on home nebulization and their proper monitoring directly or through a self management plan is recommended for better results. (UPP)
- It is recommended that those with comorbidities (such as diabetes and cardio-vascular diseases), especially the elderly must be watched more carefully and they may need special attention and care. (UPP)
- Nebulization therapy, which has always had less attention compared to pMDI and DPI, is recommended to be studied more thoroughly as home nebulization is attaining more popularity. (UPP)
- Physicians have to decide the duration of nebulization therapy in individual cases (UPP)

Q 5. What are the difficulties and problems that a patient is expected to face during the use of domiciliary nebulization therapy?

Evidence statement:

- During home nebulization therapy some of the problems faced by the patients include assembling the nebulizer; filling of the reservoir; failure to define endpoint to stop nebulization; failure to hold breath for few seconds before exhaling; problems related to cleaning and disinfection; and having reliance on the caregivers in elderly patients.
- The other problems include side effects of the therapy, both local and systemic, most commonly seen are tremors and eye complications.

Recommendations:

- Adequate training and instructions for proper use of nebulizer must be given properly to the patient and/or attendant/caregiver, including assembly, filling drug, end point of nebulization, cleaning, disinfection, and maintenance. (UPP)
- Side effects must be closely watched, especially in the elderly population which commonly include tremors and eye problems. Mouthpiece instead of facemask as an interface, amongst elderly, is recommended to prevent the eye complications (UPP)

Q 6. What is the frequency of assessment and monitoring of patients?

Evidence statement:

- The diagnosis, response and technique of use of nebulizer needs to be checked during the initial two weeks of therapy
- Thereafter periodical assessment of patients is to be done in terms of effectiveness and adherence to the treatment, the technique of use, side effects to therapy, and need for continuing nebulization.
- Possibility of re-introducing hand held inhalers as and when possible should also be looked for.
- The assessment must be both subjective (visual analogue scale) and objective (spirometry or alternatively peak expiratory flow rate). It has to be done fortnightly for the first month, then monthly for 6 months, then every 6 months and as and when required.

Recommendations:

- It is recommended to re-check the diagnosis, response, and technique during the first two weeks and thereafter periodic assessment of patients be done for the treatment efficacy, side effects, adherence, and technique (III B).
- The assessments are to be done subjectively on a 0 -10 visual analogue scale (0=perfectly well; 10=extremely unwell] and objectively in the form of spirometry or alternatively by peak expiratory flow rates. (III A).
- These assessments are recommended to be done fortnightly for the first month, monthly for next 6 months, and then every 6 months and as and when required. (UPP)
- The need for continuing nebulization should also be done periodically and attempts be made to re-introduce handheld inhalation devices as and when it is possible. (III B)
- Patients and caregivers should be educated about the proper use of nebulizer designated for the patient. (UPP)

Q 7. How to clean, maintain and service the equipment at home?

Evidence statement:

- Cleaning, disinfection, storage, maintenance, and timely servicing of the nebulizer along with its accessories, are necessary to prevent pathogen colonization and for proper functioning of the equipment.
- Cleaning of all the accessories except tubing is done with warm water, or mild detergent solution. Thereafter, they are rinsed and air dried. Outer surface of the tubing and compressor are wiped with a clean cloth. It is advised not to use a brush for cleaning which may damage the equipment. Specific instructions related to the type of nebulizer are given in Table 1.
- Nebulizers for bronchodilator therapy need to be cleaned at least once a day; and for antibiotics after each use; and boiled for 5-10 min with little detergent after every 30 uses. New nebulizers and those which have not been used for a long time should be cleaned and disinfected before use.
- The equipment should be cleaned in a smoke and dust-free location, away from open windows. Clean the equipment after house-cleaning (especially after vacuuming and dusting)
- Disinfection of mouthpiece or mask, and chamber after cleaning is done to eliminate colonization of microorganisms. A dishwasher can also be used as an alternative for cleaning and drying.
- Different organizations have recommended different methods for disinfection which include: soaking in vinegar solution (1 part vinegar and 3 parts water) for 20 minutes followed by rinsing and air drying; or spraying/rinsing in ethanol 70%; or boiling for 5-10 minutes. This should be done every 3rd day or at least every week. Ethanol is preferable over acetic acid.
- Storage of the air compressor, covered with a clean towel, is done on a sturdy surface, but not the floor. All the nebulizer parts are stored in a small bag between treatments.
- The compressor is serviced annually with replacement of the filter. Consumables, mouthpiece, mask and tubing should be replaced regularly at 3–6 monthly intervals.
- Manufacturer's instructions, wherever available, should always be followed.

Recommendations:

- Cleaning of all the accessories of nebulizer is recommended to be done with warm soap water or mild detergent solution, or by using a dishwasher; preferably after each use in case of antibiotic or after the last use of the day for bronchodilators. Thereafter, it should be air-dried and stored properly. [III A].
- Disinfection of the equipment is recommended after every 3-7 days preferably by using 70% ethanol; or soaking in acetic acid (vinegar) in water (1:3) for 20 minutes; or boiling for 5-10 minutes. Tap water should not be used. [III A]
- Always clean the equipment in a smoke and dust-free place away from open windows preferably after house-cleaning (UPP).
- Store the air compressor on a sturdy surface, not the floor, covered with a clean towel and all other parts in a bag. (UPP).
- The compressor is serviced annually with replacement of the filter. Filters should be checked monthly and changed earlier if discoloured. Consumables, mouthpiece, mask, and tubing should be replaced regularly at 3–6 monthly intervals. Manufacturer's instructions, wherever available, should be followed (UPP)
- Disposable nebulizer chambers should be replaced every 3 months while durable chambers can last up to a year if cleaned adequately [UPP].

Q 8. What is the need for infection control measures with domiciliary nebulization and which measures are to be taken ?

Evidence statement:

- In practice most of the domiciliary nebulizers are not cleaned regularly and properly, and most (73%) are found contaminated with microorganisms at >100 colony forming units/plate and a substantial number (30%) have potentially pathogenic bacteria or fungus. Home nebulizer use has been found associated with a 28.5-fold greater chance of bacterial contamination.
- Organisms found to contaminate nebulizers include bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus, multidrug resistant Serratia marcescens, Escherichia coli, multi-resistant Klebsiella species, Enterobacteriaceae, *Acinetobacter species, Micrococcus species* and fungi such as Fusarium oxysporum, and Candida species. In general fungal contamination has been less explored than others
- There is a higher probability of infective COPD exacerbations (3.3 per year) in the group where pathogens were isolated in the nebulizers compared to the group where only non-pathogenic organisms were isolated (1.7 per year) and the same could be true for patients with CF as well as other patients.
- It has been said that the nebulizer drug solution should be freshly reconstituted before every usage and the remnant solution should be discarded after use. The nebulizer chambers should not be shared.
- Regular washing, drying, and disinfection of the equipment prevents colonization of microorganisms. A smoke-free, dust-free, and non-humid location be chosen for this purpose, away from open windows and after house-cleaning. Nebulizer should be run empty for a few seconds before next use.

Recommendations:

- Improper and inadequate cleaning and disinfection of home nebulizers and their accessories often leads to contamination with bacterial, both pathogenic and non pathogenic, Gram positive and Gram negative; and fungal organisms. Home nebulizers particularly have several fold greater chances of contamination. (IIIA)
- These are recommended to be regularly and properly cleaned, disinfected, and dried to avoid contamination

with a wide variety of microorganisms. Gram-positive bacteria and fungal flora are easily eradicated, however, Gram-negative organisms are difficult to remove. (IIIA)
- Regular cleaning and disinfection of nebulizers prevent infections, such as infective exacerbations of COPD, cystic fibrosis, from the organisms colonized in these nebulizers. (IIIA)
- It is recommended to use only freshly reconstituted drug solution and remnant solution should be discarded after use. The nebulizer chamber should be given a dry run for a few moments before use and it should not be shared. (UPP)
- Nebulizer should be kept in a smoke, dust and moisture free environment away from open windows. Tap water should not be used for cleaning and outdoor drying of parts should be avoided (UPP)

Q 9. Does education really make any difference in treatment outcome?

Evidence statement:

- Patients or caregivers face several difficulties related to the management of domiciliary nebulization.
- Education related to nebulization therapy to the patient and/or caregiver, improves compliance, efficacy, quality of life and the outcome; minimizes wastage of drug; and improves the cleaning and maintenance of the equipment.

Recommendations:

- Patient and/or caregivers education is a very important component of home nebulization programs. (UPP)
- It is recommended that the patient and caregiver should be properly educated about the domiciliary nebulization which improves treatment compliance, efficacy, quality of life and outcome; minimizes drug wastage; with better cleaning and maintenance of the equipment (III A).

Q 10. Who should take the responsibility of educating the public and health care workers?

Evidence statement:

- Previous experience with untrained nurses or inexperienced doctors in educating patients regarding MDI and DPI inhaler techniques has been poor and they were not found suitable for this task.
- An "Inhaled therapy coordinator" has been recommended by BTS and ERS to take up this responsibility and doctors, nurses or physiotherapists with adequate knowledge and experience in nebulization therapy can be assigned this job. They should also provide education to other healthcare professionals, patients and caregivers.
- The "Inhaled therapy coordinator", besides education, should also provide an assessment and support service for patients at their home to improve proper usage and compliance.
- Nebulizer at the time of purchase must accompany an instruction manual for proper usage of the machine.

Recommendations:

- Untrained health care professionals should not be assigned the job of educating and training the use of nebulization therapy (IIIA)
- Doctors, nurses, and health care professionals (HCP) with adequate knowledge in nebulization therapy are recommended to be given the responsibility as 'Inhaled therapy coordinator' and assigned the task to educate other HCPs, patients, and caregivers. (UPP)
- It is also recommended that 'Inhaled therapy coordinator' should provide an assessment and support service for patients at their home for the optimal utilization of nebulization therapy (UPP)
- Manufacturer must also provide an instruction manual for proper use of a nebulizer at the time of purchase. (UPP)

Q 11. Whom to educate for home/domiciliary/maintenance nebulization?

Evidence statement:

- Focus of education on home nebulization therapy should be on the patient who has the capability to be trained; and in case of young children, patients of low IQ, debilitating patients; caregivers need to be educated for proper delivery of the therapy.
- There is no definite guidance for selection of a caregiver, however, this may be a family member or a professional health care personnel having good physical and mental health. Caregivers have been found to suffer from a gradual health breakdown, depression, and mental stress which is likely to impact a patient's health.

Recommendations:

- The emphasis of education on home nebulization is recommended primarily to be on the patient, and in case he or she is not found suitable physically or mentally, it should be on the caregiver. (UPP)
- A caregiver, in good physical and mental health, with a good understanding, is recommended to be chosen amongst the family members or alternatively may be a professional health care personnel. (UPP)
- Health related issues of the caregiver must also be addressed properly. (UPP)

Q 12. What are the follow up timings for patient's education (frequency of education)?

Evidence statement:

- There are no recommendations in the literature about the follow up timings for the patient education. This should be at regular intervals, matched with the patients' follow up visits, which may improve patients' adherence and compliance.

Recommendations:

- The timings of a patient's education are recommended to be at the time of assessment and monitoring of the patient, that is, fortnightly for the first month, monthly for the next 6 months, and then six monthly and also as when required in between.(UPP)

Q 13. What are the topics for education to be focused for patients, caregivers, and health care workers?

Evidence statement:

- There should be individual training modules for doctors, health care workers, patients and caregivers. Those modules should include detailing on the parts of the nebulizer and the nebulization technique; the medication; care of the equipment including cleaning, disinfection and maintenance; warning signs, etc.
- Sample modules for various categories have been provided. These modules help provide a uniform education pattern for every category and these can be modified also according to the local requirements.

Recommendations:

- The topics for the education of the patients, caregivers and health care workers should include the details of equipment, drugs and dosages, technique, cleaning, disinfection, maintenance, and emergency action plan for acute exacerbation etc. [UPP].
- The topics for the education of the doctors should include inhalation devices, types of nebulizers, indications of home nebulization; drugs, dosages, and side effects; technique of use, duration and difficulties; cleaning, disinfection and maintenance; assessment and monitoring; emergency action plan; patients/caregivers education; and follow up etc. [UPP].
- Modules for various categories have been provided which are recommended to be modified according to the local conditions and requirements. [UPP]

Section – VI (Group – F): Nebulization therapy in COVID-19 pandemic and in patients of other contagious viral respiratory infections

The current global pandemic of coronavirus disease 2019 (COVID-19) caused by a novel Coronavirus named SARS-Coronavirus-2 (SARS-CoV-2), has been responsible for many cases and deaths across the world. The virus is transmitted from a patient to others in the vicinity through aerosols generated from the infected respiratory mucosa and released into the atmosphere by breathing, talking, coughing, and sneezing. Transmission of SARS-CoV-2 to health-care personnel (HCP) and others through aerosol-generating procedures (AGPs), including frequently used nebulization therapy, is of great concern.

Presently, there does not exist adequate evidence either to support or oppose the risk of transmissibility of SARS-CoV-2 during nebulization in COVID-19 patients or their suspects with or without OAD. Similar problems and doubts are also foreseen in other contagious respiratory viral infections which are either emerging or which have existed in the past including influenza, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome(MERS), and infections caused by other viruses.

Not much information is yet available on SARS-CoV-2 on issues of transmission of infection, however, information related to SARS-CoV and MERS-CoV which are closely related to SARS-CoV-2, has also been useful to provide some guidance in sorting out these controversies. According to the available current information, the risk involved with nebulization in the COVID-19 cases in transmitting the infection to the HCP and bystander hosts is low. There is also not sufficient evidence to classify nebulizer therapy as an AGP, for the transmission of SARS-CoV-2, and requires more research. However, it is also equally important to undertake preventive measures to safeguard against even this small risk of transmission. As the current COVID-19 pandemic prolongs, more useful data will be generated, which may provide better information on this issue in the future.

Here, we are making certain observations and recommendations, in this chapter, based on all the current information and evidence available, related to these issues, which may be useful in the nebulization therapy during this COVID-19 pandemic and during similar situations arising in the future, with other viruses. This chapter provides most of the information available in the present time on the risk of transmission of infection from nebulization in these cases, precautions to be taken to minimize this risk while nebulizing such cases and other related issues.The evidence statements and recommendations pertaining to each of these questions are mentioned below:

Q 1. What are the important contagious viral diseases of the respiratory tract; which epidemics and pandemics have occurred during the last decades; and what are the emerging high-risk viruses?

Evidence statement:

- Contagious viral infections of the respiratory tract are many and these are on rise and are also more frequently encountered now. These have led to several epidemics and pandemics in the past with considerable morbidity and mortality.
- Global factors such as growth in human population, urbanization, interactions between human and animals, climate change, and increases in travel and trade have been responsible for emerging respiratory viral infections during the recent past

- Various contagious respiratory viral infections affecting humans include Influenza viruses, Corona viruses, Adenoviruses, Human metapneumoviruses, Respiratory Syncytial viruses, and Rhinoviruses, with influenza virus being the commonest.
- Four pandemics that occurred earlier included Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968) and pandemic influenza A(H1N1)pdm09 in 2009
- The recent emergent respiratory viruses jumping the species barrier and causing human infections include H9N2 (Hongkong 1999); SARS-CoV (Hongkong 2003); H7N7 (The Netherlands 2004); H3N2 (Canada 2005); H1N1 (Mexico 2009); MERS-CoV (Saudi Arabia 2012); H7N9 (China 2013); and SARS-CoV-2 (China 2019)
- The current pandemic of COVID-19 caused by SARS-CoV-2 has been responsible for an extremely high morbidity and mortality globally.
- SARS-CoV-2 and several other existing and emerging viruses carry a risk of infection to HCP through man-to-man transmission and/or through aerosol generating procedures (AGPs) performed over infected patients at home, medical facilities, or hospital.
- These emerging or re-emerging zoonotic RNA viruses, many on WHO priority list, that pose a high risk of infection to HCPs during AGPs performed include mostly - Arenaviridae; Hantaviridae, Nairoviridae, Phenuiviridae; Coronaviridae; Filoviridae; Orthomyxoviridae, and Paramyxoviridae
- Infection control measures must be properly followed against these viruses to protect the contacts (patients, HCP, and hospital visitors) who are at an increased risk of nosocomial infections.

Recommendations:

- Patients suffering from contagious respiratory viral infections need to be identified to prevent transmission of the infection to HCP and other contacts by taking adequate preventive steps. A large variety of viruses can be responsible for these contagious infections [UPP]
- The spread of infection from these contagious cases occurs, both, from man-to-man transmission and through AGPs performed on these patients, which require adequate control measures to prevent transmission of infection. [3A]
- Viruses that pose high-risk mostly belong to families of coronaviruses, orthomyxoviruses, and paramyxoviruses, however others - Arenaviridae; Hantaviridae, Nairoviridae, Phenuiviridae; Filoviridae also belong to same category. Not all these have human-to-human airborne transmission, but some only have the potential for nosocomial transmission due to AGPs [UPP]
- There must be preparedness to deal with the epidemics and pandemics occurring in the future with the current or new emerging or re-emerging respiratory viruses to prevent morbidity and mortality in the population. [UPP]
- A regular surveillance for new emerging viral infection must be done allowing adequate and timely intervention to prevent their spread and spill over from animal hosts to humans and later human-to-human transmission. [UPP]

Q 2. What are the physical characteristics; aerodynamic and dispersion properties; and fate of the aerosol generated by an infected patient during breathing, talking, coughing, sneezing and during their nebulization with reference to the transmission of infective organisms?

Evidence statement:

- Contagious viral infections from an infected patient spreads through aerosol generated from respiratory secretions. The aerosol deposition in the respiratory tract, in a host, is governed by their aerodynamic characteristics and by various deposition mechanisms.
- The particle size generated through talking, coughing, sneezing etc. and through Aerosol Generating Procedures (AGPs), in a patient, may be large (droplets) or small (droplet nuclei or aerosol), and the amount of aerosol generated is variable depending on the maneuver/procedure, and is also variable in between the patients with some acting as "super producers"
- The amount of aerosol generated while sneezing is maximum (Few hundred thousand to a few million), followed by coughing (Few hundred to many thousand) and is minimal while talking (Few dozen to few hundred or a few thousand)
- Larger particles (>5 μm) are filtered and deposited mostly in the nasopharynx where the virus enters into the mucous membrane of the host to replicate, spread, and produce disease. Particles in the range of 2.5 - 5 μm are deposited in the trachea, while fine (≤2.5 μm) and ultrafine particles (≤0.1 μm), reach deep into the lungs, to be deposited in the alveolar ducts and sacs.
- The large droplets (>5μm) drop down within 3 to 6 feet of origin, infecting people in this spray zone either through inhalation or through "droplet/contact spread" from touching the surfaces thus contaminated.
- The specified distance of 3-6 feet is not evidence based and has been found to be variable up to 27 feet. SARS-CoV-2, SARS-CoV-1 and MERS are transmitted mainly through droplets; however, airborne infection cannot be denied.
- The small droplets (≤5μm) evaporate rapidly to convert to droplet nuclei, light enough to remain suspended in the air for hours depending on several environmental factors and travel longer distances and are responsible for the 'airborne transmission' of disease.
- Transmission of infection through aerosols depends on their size and numbers; the concentration,viability and virulence of the virus in the aerosol; initial velocity; ventilation pattern; environmental factors; and the health and immunity of the host.
- Majority of transmission of infection occurs among people who are in close contact with the patient getting exposed to larger droplets, which drop down rapidly and at shorter distances.

- Though the virus may remain viable in the atmosphere and on different surfaces for a variable period, their concentration drops with the passage of time, thus the infectivity too. Merely the presence of viral RNA in air does not confirm infectivity.
- A medical mask and maintaining 6 feet distance is adequate to prevent infections with larger droplets whereas small size aerosols would require N 95 respirators and 6 feet distancing will not provide sufficient protection.
- Besides the aerosol generated by the patients in large quantities, AGPs further contribute to the risk of transmission of infection to the HCP, not only through further aerosol generation, but also often requiring close proximity to the patient
- Aerosols generated through AGPs have variable viral contents according to the organ and type of procedure. Nebulizers mostly generate a size range of 1-5um that has the potential to carry pathogens into the lungs, however, their role in transmission is not yet certain.

Recommendations:

- Aerodynamic properties of an aerosol and particulate deposition mechanisms govern the fate of aerosols inside the respiratory tract after their inhalation. It is recommended to study and understand the transmission dynamics of various contagious infections to help plan preventive strategies. (III B)
- Protection is recommended against droplets (large size) and droplet nuclei (small size) in cases with SARS-CoV-2, SARS-CoV-1, MERS, and other viral contagious infections. Both types of these aerosols are produced by talking, coughing, sneezing etc. and through AGPs performed on patients. (III A)
- SARS-CoV-2, SARS-CoV-1 and MERS are transmitted mainly through large droplets, however, airborne transmission can not be denied. Medical masks are recommended for protection against the large droplets and N-95 respirators for the smaller droplet nuclei. [III B]
- A minimum distance of 3 -6 feet, but preferably longer, is recommended to avoid infection through larger droplets from an index case and surfaces in this spray zone need to be disinfected properly to prevent infection through"-droplet/contact spread". Distancing may not be useful in small size aerosols.(III A)
- The airborne transmission of infection through aerosols, that remain suspended in the air for hours and travel longer distances, is governed by several factors including their number, viability, and virulence of the virus; aerosol characteristics; environmental factors; ventilation pattern; and the health and immunity of the host. Preventive steps are recommended against this mode of transmission (IIIA)
- Factors that govern the dispersion and transmission of contagious infection must be optimized for better infection control (III B)
- Aerosols generated by nebulization, an AGP, are in the respirable range (1-5um) and can reach deep into the lungs but are unlikely to carry viruses and are considered relatively safe. However, it needs to be considered as a potential risk factor for transmission of infection (III A)
- Precautions are recommended to be taken even against this potential risk while nebulizing infectious patients. Further research and studies are needed to establish the status of nebulization in spreading the infection to HCWs and others. (III A)

Q 3. What are various aerosol generating procedures and how much is the risk of transmission of SARS-CoV-2 and other contagious viral infections from nebulizer therapy?

Evidence statement:

- Transmission of infection from patients of SARS-CoV-2 or other contagious viral infections occurs through bio-aerosols produced by patients during breathing, talking, coughing, and sneezing; and also through aerosol generating procedures (AGPs) used on them.
- Enough supporting data is yet not available on the potential of nosocomial infections through these AGPs, used for various diagnostic or therapeutic purposes, and the risk of infection is also quite variable between them. Some of these procedures even produce higher concentrations of aerosols than the patient himself.
- The aerosol produced by these AGPs may be in the form of large droplets or small droplet nuclei generated by the procedure itself and also partly through induction of cough or sneeze in the patient.
- These AGPs, besides producing aerosols, also enhance the possibilities of HCW and others contracting infection by coming in close contact with the patient (through airborne route or their fomites) making it difficult to differentiate between the two.
- Various AGP's with the potential to generate aerosols from the respiratory secretions or handling of the infected tissues, in different ways, have been enlisted in the table-2, however, developing a comprehensive list is difficult in absence of supportive data and expert consensus.
- The AGPs can be grouped into two, one where procedures themselves create and disperse aerosols mechanically and in the other these procedures induce the patient to produce aerosols like in bronchoscopy or tracheal intubation.
- The exact mechanisms of generation of bio-aerosols in the respiratory tract remains unknown and various mechanisms have been proposed. There are several factors also associated with AGPs which increase the risk of transmission placing them in the category of "High-risk", and some as "Doubtful" AGPs.
- Limited data is available on nebulization, one of the AGPs, creating an uncertainty on its ability to generate infectious aerosols and thus also the risk of transmission of infection even though a high volume of aerosols (<10 μm) is generated.
- Nebulization, presently, is considered to carry a lesser infective risk since the aerosol is not patient-derived but is produced from fluid in the nebulizer chamber (medical aerosol), hence, does not carry virus, unless contaminated with respiratory secretions of the patient (bioaerosols generated during coughing or sneezing).
- In absence of proper evidence it has neither been possible to establish a link between nebulization therapy and

transmission of infection to the contacts nor it has been proved to be a safe procedure. Further research is needed to establish this fact.

- Presently, it is recommended to continue use of nebulizers, however, isolation of such patients, and taking all possible infection control measures and preventive steps, is advised, whether at home or in a medical facility.
- Technologically advanced nebulizers such as VMN, breath-enhanced, breath-actuated and those with reservoirs are relatively safer, either due to a short nebulization time or by generating aerosol only during inspiration or aerosol getting collected in a reservoir. Placing a filter at the exhalation port makes it more safe.
- Mouthpiece as an interface is safer and use of facemask is not recommended.
- Presently, it is difficult to ascertain whether the possible risk of transmission due to nebulization is causally related to the use of a nebulizer or due to increased contact between the infected person and the HCP administering the treatment. The increased exposure time of HCP to the infected person also contributes to the risk, both through airborne route and transmission through fomites.

Recommendations:

- The infection from SARS-CoV-2 or other contagious viral infections are spread through bio-aerosols produced by patients and through aerosol generating procedures (AGPs) performed on them. Adequate preventive measures are recommended to be taken against them. (III A)
- Cautious use of various AGPs is recommended in these patients since these have a potential to transmit infection to health care personnel (HCP), however, the risk is variable in between different AGPs (III A)
- The AGPs besides producing aerosols on their own also sometimes cause induction of cough or sneeze producing bio-aerosol contributing to the transmission of infection. (III A)
- The AGPs also allow close contact with patient enhancing chances of infections through aerosols and fomites requiring adequate preventive measures (III A)
- The aerosol generated from nebulizer treatment carries a lower risk of infection since it is not patient-derived (bio-aerosols) but is produced from fluid in the nebulizer chamber (medical aerosol), and hence, does not carry viral particles. (III A)
- Presently, it is recommended to continue use of nebulization, even though it is included as one of the AGPs, since no definite link has been found between use of nebulization and increased risk of transmission of infection. However, it is considered to carry a potential risk of transmission of infection. (III A)
- It is recommended to take proper preventive steps during nebulization as the possible risk of transmission due to nebulization may not only be causally related to the use of a nebulizer but also due to increased contact and contact time between the patient and the HCP administering the treatment through patient's generated aerosol and fomites (III A)
- All types of the nebulizers can be used; however, preference be given to technologically advanced nebulizers such as VMN, breath-enhanced, breath-actuated and nebulizers with reservoirs, which are considered relatively safer. It is also recommended to use an additional filter at the exhalation port (III B)
- Use of mouthpiece as an interface for aerosol therapy is recommended while nebulizing infected patients, especially with the use of jet nebulizers. Use of face mask is to be avoided due to increased risk of transmission of infection (III B)

Q 4. How to minimize the potential risk of transmission of infection during nebulization in infected cases at hospital and home?

Evidence statement:

- Aerosol generating procedures in patients of SARS-CoV-2 or other contagious viral infections often pose a threat of transmission of infection to the HCPs and others.
- Various international organizations in the present time do not classify nebulization as one of the AGPs responsible for the transmission of SARS-CoV-2 or other contagious infections in absence of definitive evidence, however, they recommend adopting infection control measures and sanitization protocols during its use because of the potential risk of infection.
- It is also not ascertainable whether the possible risk of infection in these patients is causally related to nebulizer use or due to increased contact between the infected person and HCP.
- The preventive measures to be adopted during nebulization in infected patients include use of personal protective equipment (PPE), including N-95 or higher version respirator masks, double gloves, eye protection; and following other instructions mentioned in the box; both in health care settings and at home.
- Appropriate inhalation devices are to be selected on the merits in individual cases and indiscriminate use of nebulizers is to be discouraged and restricted only to those cases where other hand-held devices cannot be used.
- Nebulizer use at home in patients with contagious disease or their suspects should also follow routine infection control measures and undertaking extra precautions like selecting a place in areas of increased air circulation with no recirculation into home (porch, patio, or garage), where dependent surfaces are easily cleanable; presence of no or limited number of persons, HCP if present to use PPE kit, strictly following sterilization protocols.
- Telehealth should be considered as an option to monitor infected or suspect patients taking treatment at home.
- Nebulization in cases of asthma, COPD, or other ailments in non-infected patients, at home or hospital, during pandemics, need no specific restrictions and should continue with required drugs including inhaled corticosteroids

Recommendations:

- Though no definitive evidence is available for the spread of infection through nebulization in patients of SARS-CoV-2 or other contagious viral infections, it is recommended to

be considered as a potential risk and precautions and preventive steps need to be taken accordingly. [III A]
- While administering nebulization to these patients in healthcare settings, strict adherence to measures that protect HCP (mentioned in the box) are recommended including stringent sanitization protocols and use of appropriate PPE. Nebulization should preferably be done in airborne infection isolation rooms (AIIR) or negative-pressure rooms a [III A]
- It is recommended that home nebulization in COVID patients or their suspects may be continued with special attention to enhanced nebulizer hygiene; to be used at a place of increased air circulation without re-circulation into the home; where dependent surfaces are easily cleanable; and in absence of people or only bare minimum possible [III A]
- Indiscriminate use of nebulizers in general must be avoided and wherever feasible and appropriate other handheld inhalation devices be used. The technique of use of these devices must be proper. [UPP]
- Telehealth could be a good option to evaluate and monitor these patients at home and smartphones can be used for this purpose. (UPP)
- Nebulization in non-infected patients at home or hospital during pandemics is recommended to be continued in the usual manner with the prescribed drugs.(UPP)
- Sharing of nebulizers is not recommended. Hospitals and healthcare facilities should preferably use single use nebulization units. (UPP)

Q 5. Are there any special precautions to be taken while nebulizing a patient with COVID-19 on mechanical ventilation, or non-invasive ventilation or on high flow nasal cannula (HFNC)?

Evidence statement:

- Many of the patients with SARS-CoV-2, SARS-CoV, MERS or other viral infections, develop respiratory complications and some may need intensive care including mechanical ventilation, or NIV or HFNC and simultaneously may also require nebulized medications.
- For intubated patients requiring nebulizer treatment, in-line nebulizer as a part of the closed circuit, should be used to keep the circuit intact preventing transmission of infection to HCP. Use of nebulizers and pMDI is to be avoided which require breakage in the ventilator circuit. Among nebulizers, if required, a VMN is preferred over jet nebulizers, preferably with a medication reservoir, with their placement prior to the humidifier
- Use of HEPA filters in the expiratory limb of the ventilator circuit is useful in capturing the exhaled aerosol, reducing the second-hand exposure to HCPs, thus preventing the transmission of infection.
- Procedures such as chest physiotherapy and suctioning, simultaneously with nebulization in mechanically ventilated patients, is to be avoided which may enhance the risk of transmission of infection through cough induction. Endotracheal suctioning is preferably done by using in-line or closed system suction catheters, of any design.
- Non-invasive ventilation (NIV) is often required while managing SARS-CoV-2, SARS-CoV, MERS or other viral infections. Nebulization in patients on NIV, is done either after discontinuing NIV or by connecting the nebulizer to the mask or to the NIV circuit.
- Aerosol delivery is optimum when the nebulizer is positioned at the mask or just before the Y-piece of the double-limb NIV circuit whereas in single limb circuits it is between exhalation port and the lung.
- Combining NIV along with nebulized aerosol therapy has been shown to be more efficacious than aerosol therapy alone as seen on spirometry findings in patients with OAD, particularly asthma.
- NIV should be assumed as an AGP and proper preventive steps must be taken by the HCP to minimize risk of transmission of infection while using NIV and nebulization simultaneously.
- With the usual pressure settings in NIV, the dispersion of exhaled air occurs within 0.5 metre radius whereas higher pressures lead to a wider distribution of exhaled air. An interface with good fitting is recommended to minimise dispersion of aerosol in the exhaled air.
- The equipment, with the reusable masks and tubings, exhalation valve, headgear, and straps, must be properly disinfected after each use. Most ventilators used for NIV, are without an airflow back into it, minimizing the risk of contamination. However, a bacterial filter and superficial cleaning of the ventilator is advised.
- High flow nasal catheter (HFNC) is an important option for oxygen therapy to reduce the intubation rate and improve prognosis in patients of COVID-19 with hypoxemic respiratory failure and is preferred over NIV. However, it is also considered as one of the AGPs.
- HFNC has a higher risk of dispersion of aerosolized viruses since it does not have a closed circuit. There is paucity of evidence on the risk of infection through simultaneous use of nebulization and HFNC, though both individually, carry a potential risk.
- High-flow nasal prongs with a surgical mask on the patient's face might benefit hypoxemic COVID-19 patients without added risk of infection to the environment. Some patients not requiring high-flow oxygen may benefit from aerosol delivery while receiving low-flow oxygen via HFNC.
- Good personal protection and hygiene for HCPs is advised during nebulization in patients with SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections undergoing mechanical ventilation, NIV, or HFNC.

Recommendations:

- Use of in-line nebulizer as a part of the closed circuit is recommended for aerosol medication in mechanically ventilated patients with SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections. Use of HEPA filters in the expiratory limb of the ventilator circuit is also recommended. (III A)
- Use of nebulizers and pMDI during mechanical ventilation should be avoided since breakage in the ventilator circuit is not desired. Among regular nebulizers, VMN is to be preferred over jet nebulizers. (III A)

- Endotracheal suctioning is recommended by using in-line or closed system suction catheters, of any design, which do not require to break the ventilator circuit for upto 7 days. (III A)
- Simultaneous chest physiotherapy and suctioning is not recommended while nebulizing an intubated patient with contagious infection since it may induce cough. (III A)
- Nebulization in infected patients with hypoxemic failure, undergoing NIV, an AGP, is done by disconnecting NIV or by connecting the nebulizer to its circuit. The results are better with a combination of the two, however, the interface must be of good fitting to avoid dispersion of aerosol which is more with higher pressure settings of NIV. (III A)
- Positioning of the nebulizer in the NIV circuit, for optimal therapy, is done at the mask or before the Y piece in the double limb circuit. In a single limb NIV circuit, it is to be attached near the exhalation port. (III A)
- The NIV equipment with all its accessories must be properly disinfected after each use in these patients. While using NIV through a ventilator, mostly there is no airflow back into it, hence, the risk of infection is minimized. However, a bacterial filter and superficial cleaning of the ventilator is advised. (III A)
- High flow nasal cannula (HFNC), another AGP, is preferred over NIV, when used in these patients with hypoxemic failure. However, HFNC has a higher risk of dispersion of aerosol since it does not have a closed circuit.
- Nebulization during HFNC, is recommended to be done either separately after discontinuing HFNC, or simultaneously through HFNC prongs covered with a surgical mask on the face to prevent dispersion of aerosol in the environment. [III A]
- A recommendation on the combined use of nebulization and HFNC is difficult to make in these contagious cases, due to paucity of data, however, both are potentially infectious on their individual use. [III B]
- Health care personnels while nebulizing patients of SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections; whether on mechanical ventilation, NIV or HFNC; must use proper personal protection equipment and follow good aerosol administration practices.[III A]

Q 6. Are there any special instructions to be followed while disinfecting the nebulizer following use in SARS-CoV-2 or other contagious infections?

Evidence statement:

- Patients infected with contagious viral infections including SARS-CoV-2 transmit infection through bioaerosols generated from their respiratory tract. The survivability of these viruses has been found to be up to 3 hours in air, and variable from few hours to few days on different surfaces, but in decreasing titres, post-aerosolization.
- The nebulizer should ideally be disinfected prior to and after each treatment, in patients with COVID-19 and other contagious viral infections, incorporating the manufacturer's instructions. A single nebulizer unit must be allocated for use in a particular patient to avoid any cross infection. Preference be given to disposable units which should be replaced every 24 hours.
- Coronavirus including SARS-CoV-2 can be disinfected by heating (electric steam sterilizer, boiling-5 min., microwave-5 min., dishwasher with heating-30 min. at 158 degrees); or by soaking in lipid solvents such as ethanol (>75%), isopropanol (>70%); or treating with chemical solutions such as formaldehyde (>0.7%), povidone-iodine (>0.23%), sodium hypochlorite (>0.21%), or hydrogen peroxide (>0.5%). Use of irradiation with ultraviolet light (60 min) can also be done. Detailed instructions for cleaning and disinfection of nebulizer using physical and chemical methods have been provided.
- Healthcare personnel should adopt appropriate infection control practices while cleaning/disinfecting the equipment.

Recommendations:

- The nebulizer used by patients of COVID-19 and other contagious viral diseases are recommended to be cleaned and disinfected, before and after each treatment, by heat or chemical disinfection methods. Irradiation with ultraviolet light can also be done. Equipment manufacturer's instructions also need to be properly followed for the safety of the patient and the equipment. [UPP]
- Preference in these cases is always to be given to disposable nebulizer units which should be replaced every 24 hours. While using regular nebulizer, a single unit must be dedicated for use in a single patient and sharing should be avoided. [UPP]
- Disinfection commonly is recommended by heating using an electric steam sterilizer, boiling, microwave, or dishwasher with heating; or by soaking in lipid solvents or chemicals such as 70% isopropyl alcohol or 3% hydrogen peroxide. Other disinfectants can also be used.[UPP]
- The outer surface of the nebulizer and outside of the tubing can be wiped with alcohol. Replace the tubing if it looks dirty inside.[UPP]
- Nebulizers should be cleaned/disinfected by a caregiver adopting appropriate infection control practices [UPP]

Conflicts of interest

The authors have none to declare.

Indian Guidelines on Nebulization Therapy

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SECTION - I (Group-A)

Basic principles and technical aspects of nebulization; types of equipment, their choice, use, and maintenance

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- How to minimize the potential risk of transmission of infection during nebulization in infected cases at hospital and home?
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- Are there any special instructions to be followed while disinfecting the nebulizer following use in SARS-CoV-2 or other contagious infections?

Introduction

Inhalational therapy, today, happens to be the mainstay of treatment in obstructive airway diseases (OADs), which include asthma, chronic obstructive pulmonary disease (COPD), and is also used in a variety of other pulmonary and non-pulmonary disorders. Ability to achieve increased local concentration of drugs in the lung through inhaled route would result in a reduction in required doses and side effects compared to alternate routes of delivery.[1] In addition, the large alveolar epithelial surface can help in rapid drug absorption facilitating systemic delivery.[2] Various drugs that can be delivered through the inhalation route include, but are not limited to, short and long-acting beta 2-adrenergic agonists, anticholinergics, inhaled corticosteroids, non-steroidal anti-inflammatory drugs, mucolytics, insulin, prostacyclin, surfactant, and numerous other antimicrobials. Inhalational therapy can be achieved by pressurized metered dose inhalers (pMDI), breath actuated- metered dose inhalers (BA – pMDI), soft mist inhalers (SMI), dry powder inhalers (DPIs) and nebulizers.

Clinical studies have shown that the drug delivery is equivalent, regardless of the type of device, whether a pMDI, a DPI, or a nebulizer, provided that the patient can use the device correctly.[3] However, the need for proper hand-breath coordination, patient activation of devices, proper inhalation pattern and adequate breath-hold period can make the delivery of drugs through pMDI or DPIs cumbersome in incredibly young, elderly, debilitated or distressed patients. In addition, inability to use variable drug concentrations and doses, reaction to propellants in some patients, high incidence of oropharyngeal deposition, difficulty in determining the dose remaining in the canister (without a dose counter), and low inspiratory capacity while using DPI, may be some other problems related to these devices.[4]

Nebulizer, an aerosol generator, where the formulated drug in aqueous solution or suspension is atomized into droplets, remains the cornerstone of medical aerosol therapy in the emergency and critical care setting. The utility of nebulizers extends to home and long-term care facilities as well.[3,5,6] Nebulizers act as an effective means for delivering inhalational therapy amongst patients who lack participation and hand-eye-breath coordination like infants, small children, and the elderly.[4] National and International guidelines for the management of asthma, COPD and some other chest diseases often recommend the use of nebulization to administer drugs locally to the airways in the lungs. However, it is recognized that much of this practice may not be evidence-based and some of these practices in their current use may be ineffective or even harmful. It has also been observed that often the dose delivered to the lung can increase over ten folds just by changing from a poor nebulizer system to a highly efficient one It is also observed that only a minor fraction of drug output from nebulizer is deposited in the lungs (about 10%) and the rest goes waste.[7] An ideal nebulizer should be the one which rapidly and consistently delivers the drug in adequate concentration to the target organ in shortest duration, minimal cost, and least wastage. It is also important that the drugs used with nebulizers should be approved by the Central Drugs Standard Control Organization (CDSCO), Government of India, or the respective authorities in their countries.

Various types of nebulizers currently available include jet, ultrasonic, and mesh, and each having its own advantages and limitations.[2] Jet nebulizers which work on Bernoulli's principle operate by compressed air or oxygen to aerosolize liquid medications remain the least expensive and most used.[4] However, the drug delivery of these nebulizers may be affected by their design and model, flow rate, fill volume, solution characteristics, composition of driving gas and patient related factors like breathing pattern, positive pressure delivery, artificial airway, and mechanical ventilation.[8] Pneumatic jet nebulizer, jet nebulizer with reservoir tube, jet nebulizer with collection bag or elastomeric reservoir ball, breath- enhanced jet nebulizer, and breath-actuated jet nebulizer are various designs of jet nebulizers currently available. Numerous nebulizer models are available in the market, and the performance varies between manufacturers and between nebulizers even from the same manufacturer.[9,10]

Ultrasonic nebulizers work by converting electrical energy to high-frequency vibrations using a transducer which are then transferred to the surface of the solution, creating a standing wave that generates aerosol. Initially introduced as large-volume nebulizers to deliver hypertonic saline for sputum inductions, nowadays small-volume ultrasonic nebulizers are commercially available for the delivery of inhaled bronchodilators. However, inability to use suspensions like budesonide and risk of denaturation of proteins associated with heating of drugs during nebulization remain the major concerns.[4]

Vibrating mesh nebulizers (VMN), which are highly efficient with a minimal residual volume, move liquid formulations through a fine mesh to generate aerosol by using electricity or an in-built battery to vibrate a piezo element. The diameter of the mesh or aperture determines the size of the particles generated.[11,12]

With ever expanding technologies in nebulization, the role of nebulizers in drug delivery continues to evolve. With the advent of technically advanced, patient friendly, hand-held nebulizers, and availability of a variety of drug formulations, and newer avenues of their use; medical practitioners, respiratory therapists, and other health care personnel face the challenge of choosing appropriate devices, and drug formulations, and their appropriate use in different clinical situations.

The National College of Chest Physicians (India) (NCCP-I) recognizes that there is a paucity of guidelines on the usage of nebulizers in acute and domiciliary settings in India. Since injudicious and unscientific use of nebulizers can be associated with serious health hazards like adverse reactions to nebulized drugs, bronchospasm with aerosolization of high-density aerosol, risk of nosocomial infection with devices and other adverse outcomes, it is imperative to have a national guideline on nebulization practices to bridge the knowledge gap amongst health personnel involved in nebulization practices. These guidelines will cater to the patients and health care personnel involved in nebulization practices, to have an overall improvement in the clinical use of this therapy, enhancing both its efficacy and safety. It will provide a comprehensive approach on the use of this therapy in various disease conditions, using different medications, in different settings, using various techniques of use, and assessing the relative benefits of different available equipment. It will also serve as an educational and scientific resource for healthcare professionals as well as to promote future research by identifying neglected and ignored areas in this field. Such comprehensive guidelines on this subject have not been available in the country and the only available proper international guidelines were released in 1997 which have not been updated for a

noticeably long period of over two decades, though many changes and advancements have taken place in this technology in the recent past.

To overcome these lacunae and to standardize the nebulization practices, NCCP-I commissioned a task force consisting of eminent experts in the field of Pulmonary Medicine, from different backgrounds and different parts of the country, to review the available evidence from the medical literature on the scientific principles and clinical practice of nebulized therapy and to formulate evidence-based guidelines.

Objective

The current guidelines have been formulated with expert opinion and available evidence with intention to improve the clinical practice in the use of nebulized therapy in India. The guideline also aims to widen the applicability of nebulizer use and improve the safety, efficacy, and precision in its use.

Target audience

The guideline is aimed at all healthcare practitioners who are involved in the care of patients who deal with nebulizers such as pulmonary physicians, internists, general medical practitioners, physicians involved in critical care and emergency medicine, paediatricians, nurses, pharmacists, respiratory therapists, paramedics, and hospital specialist teams in gerontology, rehabilitation and palliative care.

Methodology

Expert panel consisting of eminent pulmonologists from varied clinical settings including medical colleges, research institutes, medical universities, defence organizations, private and corporate hospitals, consultants, and private practitioners, representing different parts of the country, were included, and divided into five groups, A to E, assigned to study different aspects of nebulization therapy (Table 1).

Table 1 – Topics identified as background work to the consensus meeting.

INTRODUCTION
(GROUP-A): Basic principles and technical aspects of nebulization, types of equipment, their choice, use, and maintenance
GROUP - B: Nebulization therapy in obstructive airway disease
GROUP - C: Nebulization therapy in intensive care unit
GROUP - D: Use of various drugs (other than bronchodilators & inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy
GROUP - E: Domiciliary/Home/Maintenance nebulization therapy, public & health care workers education

Each group included advisors, chairpersons, a convener, and expert members who were assigned to research the available scientific evidence with respect to a particular aspect allocated. Two physical meetings were convened, the first with the conveners to discuss, frame the issues and questions pertaining to different groups. Thereafter, each group studied extensively their parts and prepared a draft which was circulated amongst the group members and their suggestions and comments were incorporated. After completion of this task, a final two-day meeting of all the groups including all the panellists was convened at New Delhi, wherein Day 1 was dedicated to the meetings of all the groups individually to discuss their document thoroughly amongst themselves and to incorporate all the suggestions made by their members in the draft. On Day 2, a joint consensus meeting of all the groups was held in which presentations were made by each group to the entire task force, the drafts were discussed and deliberated thoroughly, and the comments and suggestions made were recorded. A final draft was prepared after the consensus meeting incorporating the suggestions of everyone involved in guideline making. Thereafter, all the five drafts were merged into one document which was circulated amongst all the members of the task force and relevant comments raised at this stage also were resolved in the final document prepared. All these five drafts belonging to each group A to E were designated as five sections, I to V. The entire process of the making of these guidelines is depicted in Fig. 1.

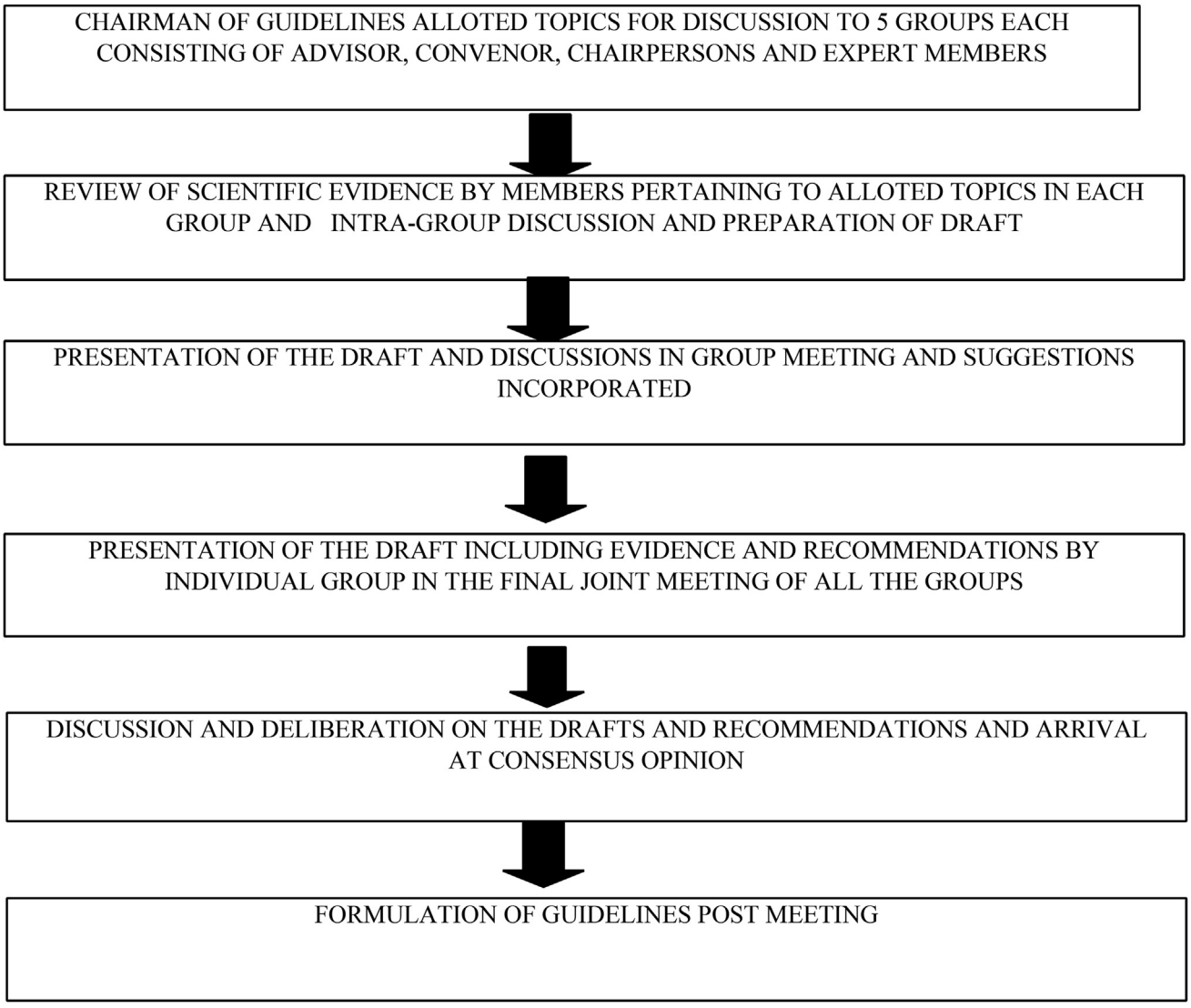

Fig. 1 – Workflow of consensus meeting and preparation of guidelines.

This guideline is based on the best available evidence (wherever available) and expert opinion. To support the guideline, a systematic search of the electronic databases was performed to identify relevant studies published. Rating of quality of evidence and strength of recommendation was done using the GRADE system (Table 2).

Table 2 – Rating quality of evidence and strength of recommendation.

Classification of level of Evidence	
Level 1	High-quality evidence backed by consistent results from well performed randomised controlled trials, or overwhelming evidence from well executed observational studies with strong effects
Level 2	Moderate-quality evidence from randomised trials (that suffer from flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or other limitation)
Level 3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations
Useful Practice Point (UPP)	Not backed by sufficient evidence; however, a consensus reached by a working group, based on clinical experience and expertise.
Grading of recommendation based on the quality of evidence	
Grade A	Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients
Grade B	Weaker recommendation where benefits and risk are more closely balanced or are more certain

Corrigendum:
Considering the present crisis due to the COVID-19 pandemic which has raised several issues and questions related to the nebulization therapy in terms of risk of the infection to the health care professionals, family members, and bystanders, it was considered necessary to add an additional Group – F (Chapter VI), to cater to the matters related to nebulization therapy during this current pandemic and/or any other similar situations arising in future due to other contagious respiratory infections. This new chapter will provide current information available on the risk of transmission of infection to contacts, how to minimize it, what precautions are to be taken and other related issues. A separate group of experts was assigned this task; related issues and questions were framed. The group collected all available evidence, and finally made their recommendations after deliberating it among all their group members. Thereafter, it was circulated among the entire task force and their comments and suggestions were incorporated in the final draft.
Chairman, Indian Guidelines on Nebulization Therapy

Section – I (Group - A): Basic principles and technical aspects of nebulization, types of equipment, their choice, use, and maintenance

Abbreviations

24 h - 24 hours
AAT - Alpha antitrypsin
ALB - Albuterol (nebulized alone)
A+FLU - Albuterol combined with flunisolide
A+IB - Albuterol combined with ipratropium bromide
A+NAC - Albuterol combined with n-acetylcysteine
A+TOB - Albuterol combined with tobramycin
BA pMDI - Breath actuated pressurized metered dose inhaler
BEN - Breath enhanced nebulizer BEN
BPD - Bronchopulmonary dysplasia
BPM - Breaths per minute
BUD - Nebulized budesonide suspension
C - Centigrade (Celsius)
CDC - Centre for Disease Control and Prevention
CDSCO - Central Drugs Standard Control Organization
CEN EN - European Committee for Standardization
CF - Cystic fibrosis
CO2 - Carbon dioxide
CONT - Continuous output
COPD - Chronic obstructive pulmonary disease
CPAP - Continuous positive airway pressure
DA - Drug admixtures
DD - Delivered dose
DNA - Deoxyribonucleic acid
DPI - Dry powder inhalers
EP - European Pharmacopoeia
FEV_1 - Forced expiratory volume in one second
FPF - Fine particle fraction
FVC - Forced vital capacity
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
GSD - Geometric standard deviation
HFNC - High flow nasal cannula
HICPAC - Healthcare Infection Control Practices Advisory Committee
ICU - Intensive care unit
I: E - Inhalation: exhalation ratio
IM - Inhaled mass
ISO - International Organization for Standardization
L/min - Litres per minute
MDI - Metered dose inhaler
mg - Milligram
mg/mL - Milligram per millilitre
MHz - Megahertz

mL (ml) - Millilitre
MMAD - Mass median aerodynamic diameter
μ (μm) - Micron (Micrometre)
μg - Microgram
NAC - N-acetylcysteine
NAMDRC - National Association for Medical Direction of Respiratory Care
NCCP(I) - National College of Chest Physicians (India)
NHF - Nasal high flow
pMDI - Pressurized metered dose inhaler
RDD - Respirable delivered dose
RF - Respirable fraction
rhDNase - Recombinant human deoxyribonucleic acid ase
RM - Respirable mass
SD - Standard deviation
SiPAP - Sigh positive airway pressure
SVN - Small volume nebulizer
TS - Nebulized terbutaline sulphate
UPP - Universal practice point
USP - United States Pharmacopoeia
VMD - Volume median diameter
VMN - Vibrating mesh nebulizers

Section-1 (Group-A) of the guidelines has been dealt under three parts as shown below:

- Part-1: Basic principles and technical aspects of the nebulization
- Part-2: Types of nebulizer equipment, their choice, and use
- Part-3: Maintenance of Nebulizer Equipment

PART 1: Basic principles and technical aspects of nebulization

PRACTICAL DEFINITIONS

MASS MEDIAN AERODYNAMIC DIAMETER (MMAD)

The diameter of a sphere of unit density that has the same aerodynamic properties as a particle of median mass from the aerosol.[13]

The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.[14]

MASS MEDIAN DIAMETER

The diameter of the particle such that half the mass of the aerosol is contained in smaller diameter particles and half in larger.[13]

GEOMETRIC STANDARD DEVIATION (GSD)

The GSD measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at 1 SD (s) from the median diameter. In a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter. Aerosols with a GSD of 1.22 are considered polydisperse. Most therapeutic aerosols are polydisperse and have GSD in the range of 2-3. It is denoted as sg or GSD.[14]

AEROSOL OUTPUT

Mass per minute of particles in aerosol form produced by the nebulizer.[13]

RESPIRABLE PARTICLES

Particles <5 μm aerodynamic diameter.[13]

RESPIRABLE FRACTION

The mass of respirable particles expressed as a percentage of the aerosol output.[13]

RESPIRABLE OUTPUT

Mass of respirable particles produced per minute (aerosol output × respirable fraction).[13]

DRUG OUTPUT FROM THE NEBULIZER

The mass of drug produced per minute as an aerosol.[13]

RESIDUAL VOLUME

This is the volume of liquid remaining in the nebulizer reservoir when nebulization has ceased. It will affect the drug output from a given fill volume.

If the residual volume is less than 1.0 ml, a fill volume of 2.0-2.5 ml may be adequate; nebulizers with residual volume of more than1.0 ml generally require fill volumes of about 4 0 ml.[13]

FILL VOLUMES

The amount of drug solution or suspension filled in the nebulizer reservoir chamber. Nebulizer chambers have different maximum fill volumes; the volume of drug solution must be known not to exceed the maximum fill volume.[13]

VOLUME OUTPUT FROM THE NEBULIZER

The volume of solution leaving the nebulizer chamber. The nebulizer output is traditionally calibrated by weighing the nebulizer unit before and after activation, assuming that no solvent is lost during nebulization by evaporation, which is not correct, invalidating this assumption. The volume output whilst useful as a general guide to nebulizer performance, it does not give precise information about the actual drug output.[15,16].

DRIVING GAS

Air can be used as driving gas except for acutely ill asthmatic patients where oxygen may be used. COPD patients should ideally receive monitored oxygen therapy while using an air-driven nebulizer system (to avoid increasing carbon dioxide (CO2) retention).[14]

FLOW RATE THROUGH THE NEBULIZER:

The flow rate of gas, whether from a compressed source or from a compressor, that drives the nebulizer chamber. It is not the same as the flow rate from the compressor, which will often be considerably higher. It is obtained by producing a pressure-flow rate curve for the nebuliser. Recordings of circuit pressure are made from zero flow (maximum pressure) to maximum flow (minimum pressure) using a rotameter, a compressor unit (or flow generator), and pressure measuring device. By substituting the nebulizer chamber for the rotameter the pressure in the circuit can be obtained with a constant flow rate from the flow generator. From the pressure-flow curve the flow rate at the nebulizer can be obtained.[17]

AEROSOL

A relatively stable suspension of liquid droplets or solid particles in a gaseous medium.

Coarse particles: 1-10 μm.

Fine particles: 0.1 −1 μm.

Ultrafine particles: < 0.1 μm.

FUME

An aerosol of solid particles, generally less than 0.1 μm in size, that arises from a clinical reaction or condensation of vapours, usually after volatilization of molten materials.

Some important issues related to the basics of the nebulization therapy have been discussed below in the form of questions:

Q 1. What is the ideal particle size for nebulization?

The particle size of bronchodilator aerosols may be important in determining the site of deposition in the lung and their therapeutic effect. The ideal particle size generated by the nebulizer depends upon the desired target site of action of the drug. We identified 2 bench, 2 non randomized and 3 randomized studies pertaining to ideal particle size. In one of the animal studies,[18] on mice and rats exposed to polydisperse aerosols of 0.5, 1.0, 3.0, and 5.0 μm MMAD, the deposition fraction was shown to increase as the particle size decreased, and that the smaller particle sizes resulted in increased peripheral deposition.[18] Another bench study on particle size distribution in an upper airway cast model of 9-month-old infant, using budesonide inhalant solution through a vibrating membrane nebulizer, observed that the optimal particle size for nebulized aerosols for inhalation therapy for infants should have a MMAD of <2.4 μm.[19]

A randomized non blinded study with terbutaline sulphate delivered by three different types of nebulizers observed that small aerosols with MMAD < 2 μm were advantageous in treatment of asthma and resulted in greater bronchodilation. The study included seven patients with mild asthma (mean FEV, 76% predicted) and results were observed over two hours after inhalation.[20] Another study by the same workers included six men with mild asthma using technetium-99m in 0.9% saline radio-aerosol concluded that small, nebulized aerosols (MMAD < 2 um) deliver a larger dose to the lungs and should be used to maximise lung deposition.[21] In a study by Mitchell et al., the distribution of radio-aerosols of two different particle sizes, MMAD of 1.4 and 5.5μm, administered from a jet nebuliser, has been studied in a non- randomized trial on patients with chronic severe stable asthma, using small increasing amounts of salbutamol (25-250 mcg total lung dose). The study did not find a difference in distribution of the aerosols within the lung or any difference in bronchodilator effect between an aerosol of small (1.4μm) particle size and an aerosol of 5.5μm in the patients.[22]

In another non-randomized trial on stable mild asthmatics, three types of monodisperse salbutamol aerosols with particle sizes of 1.5, 2.8 and 5μm, and a placebo were given as an aerosol. The volunteers inhaled cumulative doses of 5, 10, 20 and 40μg salbutamol, after which lung function improvement was determined. They found that the 2.8μm aerosol induced a significantly better dilation than the 1.5 and 5μm aerosol. Thus, it was concluded that in mild asthmatics, the particle size of choice for a beta2 agonist aerosol should be around 2.8μm.[23]

However, in two randomized double-blind placebo-controlled trials, it was observed that smaller particles achieved greater total lung deposition, but larger particles were more efficacious and achieved greater bronchodilation.[24,25] Thus, targeting of inhaled beta-agonists to the proximal airways is more important than distal alveolar deposition for bronchodilation. In one of these studies, eighteen stable mild to moderate asthmatic patients participated in a randomized, double-blind, crossover study. An aerosol generator was used to produce monodisperse albuterol aerosols of 1.5, 3, and 6μm in size, and a placebo, which were inhaled at cumulative doses of 10, 20, 40, and 100 mg. It was observed that the larger particles, 6

and 3μm, were significantly more potent bronchodilators than the 1.5μm and placebo aerosols. No adverse effects were observed in heart rate and plasma potassium. The data suggest that in mild to moderate asthmatic patients, for β_2-agonists, there may be a range of optimal bronchodilator particle sizes that deliver greatest clinical efficacy, rather than a single size per se. Notably, they have shown these to be larger 3- and 6-μm particles, in the higher part of the respirable range, rather than small 1.5-μm particles.[24] In the other randomized, double-blind, placebo-controlled study, 12 subjects with asthma inhaled technetium-99m-labeled monodisperse albuterol aerosols (30mg dose) of 1.5, 3, and 6μm MMAD, delivered at a slow (30-60 L/min) and fast (>60 L/min) inspiratory flows. Lung and extra-thoracic radio-aerosol deposition were quantified by scintigraphy. Pulmonary function and tolerability measurements were simultaneously assessed. Clinical efficacy was also compared with unlabelled monodisperse albuterol (15mg and 200mg dose) in MDI. They observed that smaller particles achieved greater total lung deposition;1.5μm (56%), 3μm (50%), and 6μm (46%); so also, the farther distal airways penetration (penetration index), and more peripheral lung deposition. However, larger particles were more efficacious and achieved greater bronchodilation FEV1 (ml): 6μm (551), 3μm (457), 1.5μm (347), MDI (494), whereas smaller particles are also more likely to be exhaled out during expiration. It was concluded that targeting regional delivery of inhaled beta2-agonist to the more proximal airways is more important than distal alveolar deposition for bronchodilation.[25]

Evidence Statement:

- The ideal 'particle size', generated by a nebulizer, depends upon the desired target site of action of the drug.
- Smaller particle sizes (MMAD< 2μm) have increased peripheral lung deposition while larger particles are associated with increased central airway deposition.
- Though smaller particles achieve greater total lung deposition, larger ones are more efficacious and produce greater bronchodilation (MMAD ranging between 3 and 6 μm). For drugs requiring peripheral intrapulmonary deposition (antimicrobials), ideal aerosol MMAD will be < 2 μm.

Recommendations:

- The ideal particle size during nebulization in a case is variable and is dependent on the target site of action of drugs to be delivered to the airways. (II A)
- The ideal aerosol MMAD recommended, while using bronchodilators in OAD, is between 3 and 6 μm. Though smaller particles achieve greater total lung deposition, the larger particles are more efficacious achieving greater bronchodilation (II A)
- For drugs requiring peripheral intrapulmonary deposition (antimicrobials), ideal aerosol MMAD recommended is < 2 μm. (II A)

Q 2. How does the flow rate, fill volume & nebulization time affect drug output?

We identified 7 bench studies and 1 randomized study addressing the above question. In one of the studies, the effect on nebulizer output on varying the flow rate and the fill volume was investigated in four brands of jet nebulizers. Raising the airflow rate from 4 to 6 1/min reduced the duration of nebulization by approximately 40%, and a further rise of airflow from 6 to 8 1/min reduced the duration by a further 15%. However, this change had only a slight effect on the proportion of the solution released. However, the fill volume directly influenced the volume released as aerosol. After a 2 ml fill, less than 1 ml was released (50%) and with 4 ml, 60-80% was released, and with 6 ml 70-85% was released. Nebuliser output fell during nebulization as the temperature of the solution dropped by 8-12 degrees C. It was concluded that a minimum 4 ml fill and an air-flow rate of 6 l/min are advocated to optimise nebuliser output.[26] Malone et al, in a study analysing the output from a jet nebulizer, using 3 different initial volume fills using albuterol, found that increasing fill volume led to significantly greater delivery of the drug which ceased completely following the onset of sputtering. They concluded that aerosolization past the point of initial jet nebulizer sputtering is unproductive.[27]

Coates et al compared two different jet nebulizers, (Hudson 1720 and Hudson 1730), with a flow rate of 6 and 8 L/min, using two tobramycin preparations (one with and one without the addition of albuterol). They found that for all solutions and each flow, the Hudson 1730 had a larger respirable fraction of tobramycin and addition of albuterol lowered the surface tension of the solution and resulted in a greater output of tobramycin. The greatest differences in the respirable fraction of tobramycin were between the 3mL fill volume using the Hudson 1720 driven by a flow of 6 L/min, which produced 8 mg of tobramycin, compared with 35 mg produced by the Hudson 1730 driven by a flow of 8 L/min. These results suggest that different nebulizers, different nebulizer solutions, and different techniques of nebulization may result in different amounts of aerosol output in the respirable fraction.[28]

Hess et al. evaluated output and respirable aerosol available to the patient (inhaled mass) using a spontaneous breathing lung model. Three nebulizer fill volumes (3, 4, and 5 mL containing 2.5 mg of albuterol) and 3 oxygen flows (6, 8, and 10 L/min) were evaluated using seventeen nebulizers. Increasing fill volume decreased the amount of albuterol trapped in the dead volume ($p<0.001$) and increased the amount delivered to the patient ($p<0.001$). Increasing flow increased the mass output of particles in the respirable range of 1 to 5 μm ($p=0.004$), but no difference in MMAD and particles in respirable range were observed between 8 and 10 L/min of flow rate.[9] The respirable mass delivered to the patient was affected to a greater extent

by nebulizer brand (p<0.001) than flow. They concluded that the performance of nebulizers is affected by fill volume, flow, and nebulizer brand.[9]

Hudson *Micromist*® nebulizer, used in a study, noted that the spray mass in droplet sizes of ≤5 μm (general respirability) and ≤3 μm (deep lung respirability) increased linearly with gas flow rate. Drug mass in the 2-6 μm range (tracheobronchial respirability) peaked at air flow rates of 8-10 L/min and decreased slightly for higher flow rates. *Micromist* with an attached reservoir (the *Hudson AeroTee*®) provided a higher dose per breath and a higher total dose by conserving the aerosol generated during exhalation. The inhaled dose increased approximately 28% compared to a standard *Micromist*®, despite significant deposition in the reservoir bag. Hence, nebulizer reservoirs could be used to attain higher doses or to utilize expensive medications more efficiently.[29]

Flow rates of 5 different compressors (3 for each compressor) tested alone and in combination with 5 different commercial nebulizers (9 of each brand of nebulizer) were evaluated using 2.5 mg albuterol solution (0.5 mL) added to 2.5 mL saline at flow rates of 2, 3, 4, and 5 L/minute. The mean flow rates for the compressors evaluated without a nebulizer attached ranged from 6.6 to 12.2 L/minute. Flow rates for the nebulizer/compressor combinations ranged from 2.08 to 5.42 L/minute. It was observed that the percentage of particles in the respirable range for one of the Jet nebulizers did not increase across flow rates in contrast to the other 4 nebulizers. Thus, marked variability exists in the flow rates among different commercially available compressors for nebulization of inhaled pulmonary medications. Different nebulizer/compressor combinations have markedly different performance characteristics which could result in different efficacy and safety profiles of the medications being administered via these devices.[30]

In another in vitro study, formoterol fumarate inhalation solution (20 μg/2 mL) was nebulized with and without ipratropium bromide (0.5 mg/2.5 mL) at different administration times (2.5–22.5 min), airflows (5–28.3 L/min), nebulizer fill volumes (2–6 mL), and nebulizer brands (Pari LC+®, Ventstream® and DeVilbiss®). It was seen that airflows between 10 and 28.3 L/min and a nebulization time of approximately 10 min appear sufficient for producing aerosols within the respirable range (1–5 μm MMAD) with the nebulizer/compressor combination used. The drug output also varied significantly ($p < 0.05$) among the three brands of nebulizers tested. Thus, administration of nebulized drugs requires proper selection of a delivery system/method for safe and effective therapy.[31] In a study by Mallol, they tried to determine the influence of altering the nebulizer flow rate and volume fill on intrapulmonary deposition of nebulized gentamicin in adolescents with cystic fibrosis (CF). It was found that using greater volume fill and higher flow rate markedly increased the intra pulmonary deposition of the antibiotic in adolescents.[32]

Evidence statement:

- Flow rate, fill volume, and nebulization time influence the production of aerosols of respirable MMAD.
- High flow rates of 6 to 8 L/min are associated with the generation of higher number of particles with MMAD in the respirable range in a short nebulization time. In case of antibiotics, using greater volume fill and higher flow rate markedly increased the intra pulmonary deposition of the drug.
- Higher fill volumes of 4 to 6 ml are associated with better MMAD particle size in respirable range but with a longer nebulization time. **A** nebulization time of up to 10 minutes is optimal or up to the point of sputtering.
- Different makes of nebulizers are associated with variable performance for a given flow rate, fill volume, nebulizer solutions, and may influence the duration of nebulization. Nebulizer reservoir bags are useful to attain higher doses and utilization of expensive medications more efficiently.

Recommendations:

- It is recommended that flow rate and fill volumes of a nebulizer must be mentioned by the manufacturer which should be taken into cognizance by the user to optimize the performance of nebulizers. (III A)
- It is recommended that a minimal fill volume of 4 - 6 ml and a flow rate between 6 – 8 L/min using compressed air may be used for obstructive airway disorders in the absence of recommendation by the manufacturer. (III A)
- The optimal nebulization time recommended is up to 10 minutes or until spluttering occurs. (III B)
- Nebulizer reservoir bags may be useful to attain higher doses and for utilization of expensive medications more efficiently. (III B)
- It is recommended that higher flow rates between 8 – 10 L/min and greater fill volumes may be used for administration of antibiotics targeting intrapulmonary deposition. (III A)

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PART - 2: Types of nebulizer equipment, their choice, and use

This part includes particulars of different types of nebulizers, their technical details and comparative evaluation; how to make a choice of equipment; how to use different formulations of drugs in solution or suspension form; issues on mixing of different drugs in the fill chamber; availability of different interfaces and their appropriate use; maintenance of the equipment etc. These issues have been discussed in the form of following questions:

Q1. What are the types and technical details of nebulizers available including their mechanism of function and comparative evaluation?

There are broadly three types of nebulizers available: the pneumatic or jet nebulizers, the ultrasonic nebulizers and the vibrating mesh or aperture plate nebulizers.

Pneumatic or jet nebulizers

The pneumatic/jet nebulizer uses 2 to 10 L/min of pressurized gas. This gas passes through an exceedingly small aperture (the jet or the venturi) to draw medication up through a capillary tube from the nebulizer reservoir in order to generate a mist with a wide range of particle sizes. These particles blast into the protruding surfaces of primary and/or secondary baffles within the nebulizer that are positioned in the path of the aerosol created so that the large liquid droplets impinge upon them removing these out of the mist and returning them to the reservoir. This allows a reduced and more useful particle size of the existing aerosol to get out.[1] The jet nebulizers are the cheapest available and allow a wide range of drugs to be nebulized; making them the most frequently used nebulizers. Substantial variances in nebulizer performance are caused by differences in their design, the source of energy (compressed gas or electrical compressor), gas flow and pressure, connecting tubing, interface used (spacer, and mouthpiece or mask), and the breathing pattern of the patient. These nebulizers need compressed gas or a compressor to operate, are generally bulky, have poor delivery efficiency, larger residual volumes and treatment times are much longer. Jet nebulizers are also available in some modified forms such as Jet nebulizer with reservoir tube; Jet nebulizer with collection bag; Breath-enhanced Jet nebulizer; and Breath actuated Jet nebulizer.

(See more details in Question No. 1, Part III of Section I).

Ultrasonic nebulizers

Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz). These sound waves are transmitted to the surface of the drug solution, resulting in the formation of the standing waves. The crests of these waves are then broken up into droplets to produce the aerosol mist.

Ultrasonic nebulizers have many limitations compared to jet nebulizers. For instance, they have large residual volumes, an inability to aerosolize viscous solutions, and degradation of heat-sensitive materials. Therefore, they should not be used with suspensions, liposomes, viscous solutions, and proteins.

Vibrating mesh or aperture plate nebulizers

Vibrating Mesh nebulizers (VMN) use micro pump technology for aerosol production. These work by vibrating a precisely drilled mesh which is in contact with the medication. The liquid form of medication is forced through multiple apertures in a mesh to generate aerosol. Mesh nebulizers can be classified into two categories:[1] active mesh nebulizers and[2] passive mesh nebulizers. Active mesh nebulizers use a piezo element that contracts and expands on application of an electric current and vibrates a precisely drilled mesh in contact with the medication to generate aerosol. Passive mesh nebulizers use a transducer horn that induces passive vibrations in the perforated plate with 6000 tapered holes to produce aerosol.

The mesh nebulizers are small and portable, powered by either battery or electricity, operate silently, have short treatment times, increased output efficiency along with a predominantly fine-particle fraction, and minimal residual volume. These are more efficient than jet nebulizers and can provide higher drug doses to patients. Due to the higher efficiency of mesh nebulizers, the dosages of drug formulations may need to be adjusted to prevent the development of adverse effects because of overdose. Therefore, patients should be monitored closely during treatment for clinical responses and side effects.

Despite many advantages there are several challenges associated with mesh nebulizers. For instance, delivery of viscous drugs and suspensions can clog the pores of the mesh, and it can be difficult to accurately determine the output of the device. The residual volume varies with the design of each device. The cost of the vibrating mesh devices is comparable to that of ultrasonic nebulizers but is much higher than that of conventional jet nebulizers. All VMN require regular cleaning to prevent build-up of deposit and blockage of the apertures, especially when suspensions are aerosolized. Table 1

Evidence statement:

- Three types of nebulizers are available: Pneumatic or Jet, Ultrasonic and Vibrating Mesh Nebulizers (VMN), all having different mechanisms of function.
- Ultrasonic nebulizers are not suitable for use in suspensions, liposomes, viscous solutions, and proteins; besides their having large residual volumes.
- The technical details and comparison between different nebulizers are given in a tabular form.
- Jet nebulizers are simple, inexpensive, and commonly used, whereas vibrating mesh nebulizers are more efficient but expensive.

Table 1 – Technical details and comparison between different types of nebulizers.

	Compressor/Jet nebulizers	Ultrasonic nebulizers	Mesh Nebulizers
Features:			
Power source	Compressed gas or electrical mains	Electrical mains	Batteries or electrical mains
Portability	Restricted	Restricted	Portable
Treatment time	Long	Intermediate	Short
Output rate	Low	Higher	Highest
Residual volume	0·8–2·0 mL	Variable but low	≤0·2 mL
Environmental contamination:			
Continuous use	High	High	High
Breath-activated	Low	Low	Low
Performance variability	Intermediate	Low	High
Formulation characteristics:			
Temperature	Decreases[a]	Increases[b]	Minimum change
Concentration	Increases	Variable	Minimum change
Suspensions	Low efficiency	Poor efficiency	Variable efficiency
Denaturation	Possible‡	Probable‡	Possible‡
Maintenance and costs:			
Cleaning	Required, after single use	Required, after multiple use	Required, after single use
Cost	Very low	High	High
Advantages and Disadvantages:			
Advantages	- Cheap - Easy to use - Effective in delivering drugs that cannot be delivered with pMDI and DPI - High doses possible	- Easy to use - Quiet - More efficient than jet nebulizers	- Most efficient - Easy to use - Quiet - Faster drug output and lesser nebulization time - Small residual volume - Most of medications can be delivered
Disadvantages	- Inefficient - Pressurised gas source/ motor and additional tubing required - Noisy - Often bulky - Difficult to clean	- Large residual volume - Not all medications possible- Inability to aerosolize viscous solutions - Degradation of heat-sensitive materials	- Costly - Requires regular cleaning - Not compatible with drugs that crystallize on drying

Adapted from References.[1-3]

[a] For jet nebulisers, the temperature of the reservoir fluid decreases by about 15ºC during nebulization because of evaporation.

[b] For ultrasonic nebulisers, vibration of the reservoir fluid causes a temperature increase during aerosol generation, which can be as high as 10–15ºC.

Recommendations:

- Choice of nebulizer is to be made between Jet, ultrasonic and vibrating mesh nebulizers according to the usage in patients (Grade IIIA)
- Jet nebulizers are recommended for common use, whereas ultrasonic nebulizers have limited uses, but vibrating mesh nebulizers are more efficient but expensive. (UPP)

Q2. How do you compare different types of nebulizers?

Multiple bench studies have compared the different types of nebulizers available. The newer aerosol devices, such as ultrasonic and vibrating-mesh nebulizers (VMN) have been shown to have a higher efficiency[4-8] and shorter nebulization time[4,8-9] compared to the conventional jet nebulizers. It has also been seen that the jet nebulizer performance is affected by the fill volume[10] and they have a larger residual volume (and the consequent drug wastage).[11] It has also been seen that the use of mesh nebulizers can not only lead to an increased pulmonary bioavailability but also increase the systemic absorption of the drugs administered.[10] Position is also an important factor for mesh nebulizer affecting the run time which is three times longer in the tilted position when compared to the horizontal position and this also leads to variability in particles distribution.[11]

The bench studies have also documented a change in the droplet size over the nebulization time with different devices which occurs because of the changing drug solution, temperature, and concentration in the reservoir.[12] With the jet nebulizer, an increase in the droplet size initially followed by a decrease, has been observed during nebulization which is attributable to reduction of the temperature by approximately 7° C during the first 2 minutes which can increase the

viscosity of the nebulization solution. After this initial period, the increasing drug concentration induced a reduction of the surface tension and, consequently, a decrease in the droplet size. In the ultrasound nebulizer, an increase in temperature of about 20° C. of the solution during the first 6 minutes has been observed leading to a decrease in droplet size, viscosity and surface tension, along with increasing the saturated vapour pressure.

In an observational study among healthy volunteers, the urinary excretion of amikacin was compared after nebulization using a jet and a mesh nebulizer. It was seen that the amikacin urinary excretion was almost twice as high with the mesh nebulizer as compared with the jet nebulizer.[13]

An open label, randomized, multicentre, cross-over trial in cystic fibrosis patients had compared the serum, sputum, and urinary concentration of tobramycin after its administration using a jet and a mesh nebulizer.[14] It was observed that the sputum and serum levels of tobramycin produced by the 90-mg dose delivered using a mesh nebulizer approximated those achieved with a 300-mg dose administered using a jet nebulizer. It was also seen that compared with the standard jet nebulizer; the mesh nebulizer safely achieved an approximately threefold greater efficiency in the delivery of tobramycin to the lungs in less than half the time. However, there were no significant differences between treatments in the form of change in FEV1, 30 minutes after dosing or in the frequency of adverse events. Nebulization time using the mesh nebulizer was less than 50% of those of the jet nebulizer. Similar findings were also seen in a recent randomized, open-label, crossover study, where nebulization of 75 mg tobramycin with the mesh nebulizer in children with cystic fibrosis was found to have similar results when compared to 300 mg tobramycin nebulized through the jet nebulizer.[15]

In a randomized, investigator blind crossover study, in moderate to severe asthma patients, the mesh nebulizer was found to be approximately five times as efficient as jet nebulizer in relative lung delivery of albuterol.[16] A recent prospective study comparing mesh nebulizer and jet nebulizer in paediatric asthma patients have reported a shorter inhalation time when using the mesh nebulizer, though the other clinical findings did not differ between the groups.[17] In another study, the prospectively identified data of all emergency department patients receiving aerosolized bronchodilator was assessed and it was observed that the use of mesh nebulizer was associated with fewer admissions to the hospital, shorter length of stay in the emergency department and a reduction in the albuterol dose.[18] In a vitro model, mimicking a 10 year old infant, the new aerosol devices, such as ultrasonic and mesh nebulizers, were found to be more efficient than the jet nebulizer.[19]

Due to the higher efficiency of mesh nebulizers, the dosages of drug formulations may need to be adjusted, when changing over from jet nebulizers, to prevent the development of adverse effects because of overdose and in such situations, patients should be monitored closely during treatment for clinical responses and side effects.[14] In one of the studies,[4] mesh nebulizer could be employed as a portable device for rhDNase therapy in patients with cystic fibrosis and it produced a higher total mass output efficiency (88%) than the jet nebulizer (68%) ($P < .001$), and total nebulization time was also shorter with the mesh nebulizer (6.1 min vs 7.2 min, $P = .03$).

In an ICU setting the jet and mesh nebulizers performed best at either the ventilator or humidifier, and worst at the Y-piece, whereas the ultrasonic nebulizer performed best at the humidifier and worst at the Y-piece. The mesh nebulizer outperformed jet nebulizers at all tested positions, and the ultrasonic nebulizer when placed at either the ventilator or the humidifier.[5] Another study in a model comparing the use of nebulizers during mechanical ventilation also found the mesh nebulizer to have higher lung dose/delivery efficiency compared with the jet nebulizer only when placed before the Y-piece.[20]

Mesh nebulizers produced greater inhaled drug dose and lowest residual dose, whereas the jet nebulizer, breath-enhanced nebulizer, breath-actuated nebulizer and manually triggered nebulizer produced lower exhaled drug dose in both in vitro and ex vivo models.[21]

Evidence statement:

- The newer nebulizers like the ultrasonic and the vibrating mesh nebulizer have higher efficiency compared to the conventional jet nebulizer, with shorter nebulization time and smaller residual volumes.
- Changes in the temperature and concentration of the drug in the reservoir may occur with jet and ultrasonic nebulizers which can influence the droplet size during nebulization.
- Mesh nebulizers have a higher drug delivery and better drug bioavailability in comparison to jet nebulizers requiring reduction in the dosages of the drugs to prevent the adverse events and its loss.
- The mesh nebulizer compared to the jet, shows improved delivery and better efficiency of bronchodilators among asthmatics reducing their admission rates and the median length of stay in the emergency department.
- Positioning of the nebulizer in the ventilator circuit in mechanically ventilated patients influences the efficiency of nebulizers and this position is variable with different nebulizers.

Recommendations:

- All the three nebulizers in the clinical practice; jet, ultrasonic, and mesh; are efficacious in the appropriate clinical scenarios and it is recommended to make a choice according to the clinical situations. (UPP)
- Mesh nebulizer is recommended as the most efficient device in terms of relative efficiency with a shorter nebulization time, smaller residual volumes, and not leading to any change in the temperature of the drug during nebulization. (II A)

- While using the mesh nebulizer, the dosage of the drug may need to be reduced and the patient be more closely monitored for the clinical response and any adverse effects due to overdosages. (II B)
- The position of nebulizers in the ventilator circuit, for their proper efficiency, is variable with different nebulizers which must be followed during usage. (II A)

Q 3. Which nebulizers are suitable for drugs other than bronchodilators and inhaled steroids?

Studies have evaluated the ability of mesh nebulizers to nebulize a variety of drugs. It has been found to effectively nebulize solutions as well as suspensions, along with liposomal formulations,[22] proteins, (such as α-1 anti-protease, dornase alfa) and antibiotics.[14,15]

Vibrating mesh nebulizers were found to be more effective in comparison to jet and ultrasonic nebulizers in a study while nebulizing liposomal formulations. The output of the nebulizers in terms of liposomal transport efficiencies differed significantly among the nebulizer types (20–100%, $p < 0.05$), with the mesh nebulizers being the most effective. The integrity of the conventional liposomes was almost unaffected by the atomization process, while polymer coated and especially positively charged liposomes showed enhanced leakage. The release rates were highest for the-mesh nebulizers regardless of the surface characteristics of the liposomes (increasing from 10% to 20% and 50% for the conventional, PEGylated and positively charged formulations, respectively). While the droplet size of the aerosol decreased with increasing salt concentration, different liposomes had no influence on the droplet size distribution.[22]

When the ability of mesh nebulizer to atomise various sizes of plasmid and cosmid DNA was assessed, it was seen that there was denaturation of non-complexed, supercoiled DNA, occurring during nebulization, which is like jet nebulizers. They compared various atomization devices including Electrostatic spray, Ultrasonic nebulizer, Mesh nebulizer and Jet nebulizer. Results varied with the device as well as DNA size. Jet nebulizer was ranked among the lowest. With ultrasound nebulizer, the DNA is destroyed. A significant loss in plasmid and cosmid DNA was also observed in the VMN despite a relatively low strain rate and a varied residence time. They found electrostatic spray to be a sound option for delivery of naked DNA (of any size) to the lungs.[23]

In a benchmark study, mesh nebulizer was found to be suitable for nebulizing rhDNase in cases of cystic fibrosis having a higher MMAD, total mass output efficacy and shorter nebulization time as compared to jet nebulizer.[4]

In an observational study with a total 20 subjects; 6 healthy, 7 with alpha antitrypsin (AAT) deficiency and 7 with CF; ~70 mg of inhaled radiolabelled active AAT, was delivered through AKITA2 APIXNEB®. This device combines a VMN with low drug residual volume and the ability to control both inhalation flow rate and inhaled volume through a computerized compressor. Post-inhalation lung and extra-thoracic deposition of radiolabelled AAT were measured. The total lung deposition of AAT was ~70% of the total dose and it was similar in all the groups and there was no impact of lung function or severity of the disease on the lung deposits. Also, large amounts of AAT could be delivered in a short time. Use of this device to inhale AAT was well tolerated with an excellent lung deposition, making it an ideal option for aerosol therapy.[24]

The survival of patients with cystic fibrosis (CF) has improved considerably over recent decades, because of better and new treatments including the use of nebulized antipseudomonal antibiotics. In a recent randomized, open-label, crossover study, nebulization of 75 mg tobramycin with the mesh nebulizer (I-neb®) in children with cystic fibrosis resulted in comparable deposition to 300 mg tobramycin with the jet nebulizer (PARI-LC Plus®). Nebulization time was 50% shorter and patient satisfaction was significantly higher with the mesh nebulizer. However, long-term safety of tobramycin nebulization needs to be monitored clinically, especially regarding the effects on tubular kidney injury.[15] Similar results were also observed in another randomized, open-label, crossover study comparing 90 mg tobramycin delivered through mesh nebulizer vs 300 mg delivered through conventional jet nebulizer.[14]

Evidence statement:

- Vibrating mesh nebulizers effectively nebulize solutions and suspensions; as well as liposomal formulations; proteins, such as α-1 antiprotease, dornase alfa; and antibiotics.
- Denaturation of non-complexed, supercoiled DNA occurs during nebulization while using mesh nebulizer which is like jet nebulizers.

Recommendations:

- The vibrating mesh nebulizer is recommended to be used to deliver a wide range of solutions and suspensions; including liposomal formulations; proteins, such as α-1 antiprotease, dornase alfa; and antibiotics. However, it can also denature non-complexed, supercoiled DNA, like jet nebulizers. (III B)

(Please also refer to Q. No. 8; Part II of Group-A for more information).

Q 4. What relevance do jet nebulizer and compressor combinations have?

The jet nebulizer consists of two important parts - the compressor and the nebulizer chamber. Marked variability exists in the flow rates among different commercially available compressors and the different nebulizer/compressor

combinations. This can lead to markedly different performance characteristics of the nebulizer and its combination with compressors, which could result in their different efficacy and safety profiles.[25-26]

In a comparative study flow rates of five different compressors tested alone and in combination with five different commercial nebulizers were evaluated. The performances of the different nebulizers were evaluated, using 2.5 mg albuterol solution (0.5 mL) added to 2.5 mL saline, at flow rates of 2, 3, 4, and 5 L/minute. Aerosols were studied by using a laser particle analyzer and time for nebulization and residual volume were also recorded. The mean flow rates for the compressors without a nebulizer attached ranged from 6.6 to 12.2 L/minute. Flow rates for the nebulizer/compressor combinations ranged from 2.08 to 5.42 L/minute. It was observed that the percentage of particles in the respirable range for the Pari LC Jet® did not increase across flow rates in contrast to the other 4 nebulizers. Such technical information is useful for selecting different nebulizer/compressor combinations.[25]

Though the manufacturers recommend the use of a consistent nebulizer/compressor combination, at times the compressor and nebulizers from different manufacturers are also used. In a bench study, a breathing simulator that mimicked the breathing patterns of an infant and a child, was used to evaluate 30 jet-nebulizer/compressor combinations available in market using 2 ml of budesonide inhalation suspension (BIS), 0.25 mg/mL. The aerosol generated was quantified by liquid chromatography. It was found that the MMAD of the aerosol ranged between 4.8 μm and 9.9 μm, The geometric standard deviation (GSD) ranged between 1.7μm and 2.1μm; and the inhaled mass of budesonide ranged from 1% to 9% (infant) and from 4% to 20% (child). Thus, there was a wide variability in the delivery of budesonide between the 30 nebulizer/compressor combinations.[26]

Another study comparing the recommended compressor/nebulizer combinations by the manufacturers and simultaneously also using all other combinations available commercially. It used a breathing simulator programmed to deliver an adult breathing pattern and the drug used was albuterol (2.5 mg/3 mL). It was found that replacing the nebulizer or compressor with a different brand changes the flow-pressure and aerosol characteristics. These changes were more prominent when the nebulizer was replaced than when the compressor was changed. They cautioned that the practitioners should be cautious when changing compressor/nebulizer pairs unless they are aware of the resulting impact on the flow-pressure and aerosol characteristics.[27]

The long-term use of compressor/nebulizers has been shown to affect the performance of the machine. This aspect was studied in one of the trials where they used four new units of compressor/reusable jet nebulizers from three different brands. These were operated for one hour twice daily five days every week for 24 weeks. Compressor flow/pressure characteristics were measured every 6 weeks. One of the four machines had statistically significant declines in pressures at each measurement with or without nebulizer, however, the maximal flow was stable over time in both with or without nebulizer, but it significantly varied among brands. All compressors-maintained baseline Inhaled Mass (IM), in respirable range, and other aerosol characteristics. Two of these units stopped working at 11 and 24 weeks. It has been suggested that the measurement of maximal flow could help in identifying the compressors that are likely to fail and need replacement. Long-term use of compressor/nebulizers affected their performance.[28]

Evidence statement:

- The available jet nebulizer can have variable performances and changing the nebulizer and the compressor combination can change the flow-pressure and aerosol characteristics. Users should be cautious when changing compressor/nebulizer pairs unless they are aware of the resulting impact on the flow-pressure and aerosol characteristics.
- It has been seen in bench studies that the long-term use of compressor/nebulizers can affect their performance.

Recommendations:

- The compressor nebulizer combination recommended by the manufacturer should be used since any variation may alter their performance. (III B)
- There is a need to check the clinical performance of the nebulizer on regular intervals with their continued use. (UPP)

Q 5. How do we select the type of machine? What are the points to be considered while choosing a nebulization device?

The appropriateness of a nebulizer for a patient in each clinical situation depends on several factors. Following points need to be considered before making a choice in a particular patient.

- In what formulation is the drug available? Is it in a solution or a suspension form?
- Compare its working in terms of ease of use and safety?
- The output characteristics, efficiency and performance of the nebulizer must be assessed before the selection is done.
- Is the device patient-friendly in terms of its operation and maintenance?
- Is the device clinically useful on a broad scale (can it be used to treat different patient populations in various clinical settings and patients in different age-groups)?
- Is the device cost effective and is it reusable?
- Can the device be used for many drugs?

- Is the device eco-friendly in terms of environmental contamination?

Fig. 1 shows the suggested algorithm for selecting the appropriate device in different clinical situations.[29]

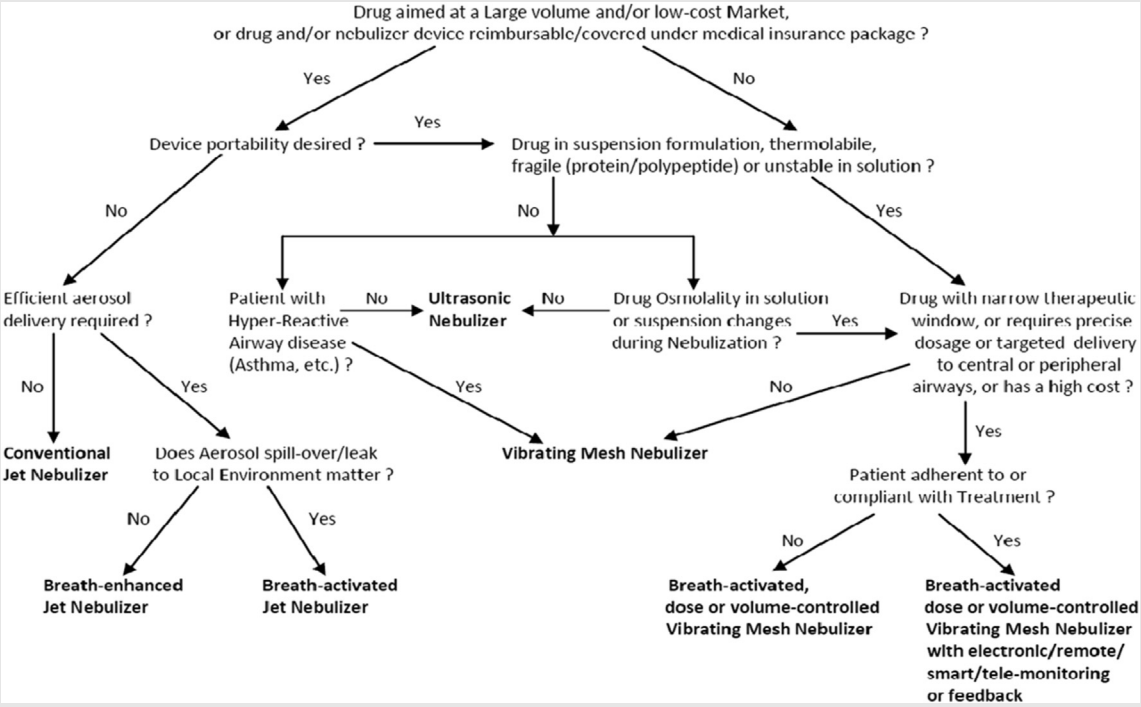

Fig. 1 – A suggested algorithm for selecting the device: Adapted and modified from reference:.[29]

Q 6. What are the quality standards available for the nebulizer performance?

Most of the developmental activities taking place on both compressor-based jet-nebulizer systems and more portable mesh-based device designs have been towards making the devices more patient/carer-friendly (faster, quieter, and less environmental contamination with drugs). However, less attention has been given to the variability of nebulizer –compressor combinations with respect to delivered dose (DD), by way of mode of operation of the nebulizer unit itself and the additional variability that could be introduced by the patient. Guidelines have been formulated towards testing of these nebulizer equipment and the important ones are mentioned below:

European Committee for Standardization [CEN] EN 13544-1

European Committee for Standardization. CEN: EN 13544-1: 2007+A1:2009: Respiratory Therapy Equipment: Nebulizing Systems and Their Components. London: British Standards Institute; 2010.

United States Pharmacopoeia [USP] chapter 1601

US Pharmacopoeia. United States Pharmacopeia (USP) 35. Rockville (MD): USP; 2012. Chapter 16.

Products for nebulization – characterization tests.

European Pharmacopoeia [EP] chapter 2.9.44

European Pharmacopoeia. European Pharmacopoeia (EP) 7.3. Strasbourg: European Directorate for the Quality of Medicines and Healthcare; 2010. Chapter 2.9.44: Preparations for nebulisation – characterization.

International Organization for Standardization [ISO] 27427:2013[E])

International Organization for Standardization. ISO 27427:2013(E): Anaesthetic and Respiratory.

Equipment: Nebulizing Systems and Components. Geneva: ISO; 2013.

The test methods of the International Organization for Standardization. ISO 27427:2013(E): Standardization for nebulizers are described in terms of delivered dose (DD), output rate, and MMAD. It is of relevance to note that the USP contained such guidance up to USP 37, but in recent updates all guidance relating to parameters to report and how to calculate them have been removed.

The ISO standard states that its objective is "to ensure that the results of the various tests declared by the manufacturer are meaningful to the users and buyers of nebulizers". The test methods recommended by ISO as already stated include DD (the total amount of drug that leaves the nebulizer and is delivered into inhalation) and DD-output rate (the amount of drug

delivered into inhalation during a minute) using a single standardized breathing pattern of 500 mL tidal volume, 1 : 1 inhalation:exhalation (I: E) ratio, and 15 breaths per minute (BPM) frequency.

The standards in form of DD and DD-output rate, represent a good basis for the direct comparison of nebulizers under in vitro laboratory conditions for quality-control purposes. They are, however, limited in that the respirable DD (RDD; the amount of drug contained in droplets of a size suitable for penetration into the lungs <5 μm) leaving the nebulizer mouthpiece during inhalation is not directly reported. Further, in ISO standards, it has also been emphasised that "the percentage of fill volume emitted is an important value to be disclosed to the user, since it influences the decisions of dosage intended for delivery in terms related to the expected amount of drug given to the patient". This statement shows an attempt to address clinically relevant parameters in the standard, but the omission of RDD or use of different patient-relevant breathing patterns could lead to incorrect decisions in terms of the expected amount of clinically effective drug delivered to the patient from a device. The results of the test methods in the standards are thus limited in their clinical usefulness, but at least it needs to be made mandatory for the manufacturers to follow these guidelines and make relevant declarations on the product in the market to guide the physicians/users in making a correct choice and its correct usage.

To improve convenience to patients, there have been advances in the operation of nebulizers, resulting in fast treatment times and less drug loss to the environment. However, limited attention has been paid to the effects of these developments on the DD and RDD. In one study, nine different nebulizer brands with different modes of operation (conventional, venturi, breath-enhanced, mesh, and breath-activated) were tested by determining DD of 5 mg of albuterol through adult breathing patterns with inhalation: exhalation (I:E) ratios between 1:1 and 1:4. Droplet size was determined by laser diffraction and RDD calculated. Between the non-breath-actuated nebulizers, a 2.5-fold difference in DD (~750−1,900 μg salbutamol) was found; with RDD, there was a more than fourfold difference (~210 −980 μg). With increasing time spent on exhalation, there were progressive reductions in DD and RDD, with the RDD at an I:E ratio of 1:4 being as little as 40% of the dose with the 1:1, I:E ratio. The DD and RDD from the breath-activated mesh nebulizer were independent of the I:E ratio, and for the breath-activated jet nebulizer, there was less than 20% change in RDD between the I:E ratios of 1:1 and 1:4. Comparing nebulizers using the I:E ratio recommended in the guidelines does not predict relative performance between the devices at other ratios. There was significant variance in DD or RDD between different brands of non-breath actuated nebulizer. In future, consideration should be given to revision of the test protocols included in the guidelines, to reflect more accurately the potential therapeutic dose that is delivered to a realistic spectrum of breathing patterns.[30]

Evidence statement:

- Various standards have been formulated by different organizations for the quality control purposes and providing technical details to guide the selection of proper equipment and provide proper instructions of its use, however, presently, International Organization for Standardization [ISO] 27427:2013[E]) seems most appropriate amongst all others.
- The parameters laid down by ISO to maintain these standards include 'Delivered Dose' (DD) and 'DD-output rate', under in vitro laboratory conditions, represent a good basis for the direct comparison of nebulizers commercially available.
- However, not including 'Respirable DD' (RDD) - the amount of drug contained in droplets of a size suitable for penetration into the lungs (<5 μm), in these parameters, is a limitation.
- It has also been emphasised by ISO that "the percentage of fill volume emitted is an important value to be disclosed to the user, since it influences the decisions of dosage intended for delivery in terms related to the expected amount of drug given to the patient."
- Though the results of the test methods in the standards have limited clinical usefulness, at least these need to be made mandatory for the manufacturers to follow and make relevant declarations to guide the physicians/users in making a correct choice and its proper usage.
- There is significant variance in DD or RDD between different brands of non-breath-actuated nebulizers and to some extent between jet and mesh nebulizers.

Recommendations:

- While making a choice of nebulizer, preference be given to those manufacturers who comply with the standards of ISO, CEN, USP, or EP; preferably ISO; and who have made declarations of the technical details on their products, as per the guidelines of that particular organization. (UPP)
- It needs to be made mandatory for the manufacturers to follow these guidelines and make relevant declarations on the product to guide the physicians/users of making a correct choice and its correct usage. (UPP)
- Nebulizers without the declarations need to be tested for required parameters before use (UPP)

(Please also to refer to Q. No. 2; Part I of Group-A for additional information).

Q7. What different solutions/suspension are suitable to be administered by the different machines?

Most nebulized drugs fall into two physicochemical categories:[31]

1. Drug Solutions: Contain a drug that is dissolved in saline or occasionally in other liquids (Cyclosporine in alcohol).
2. Drug Suspensions: Contain a drug that is not soluble in water or other respirable liquids; they exist as a mixture of small drug particles suspended in liquid.

Drug suspensions are inherently more complicated to describe as they are a mass of suspended particles which may or may not be present within the droplets which is clinically important, whereas with solutions, it is assumed that the entire drug is homogeneously dispersed throughout all droplets. It appears that a suspension is generally more difficult to nebulize than a solution. A study compared the amount of nebulized budesonide (BUD) suspension and nebulized terbutaline sulphate (TS) solution inhaled by ten healthy adults through conventional jet and ultrasonic nebulizers. The inhaled mass of BUD varied depending on the nebulizer used, whereas that of TS was unaffected by the choice of nebulizer. The median inhaled mass of BUD was 31.4% with the jet nebulizer and 9.9% with the Ultrasonic nebulizer, whereas the median inhaled mass of TS was 50% and 52% with the two nebulizers, respectively. The study showed that a suspension is generally more difficult to nebulize than a solution and that the BUD suspension should not be used in ultrasonic nebulizers. Hence, the conventional ultrasonic nebulizers cannot be used to administer suspensions.[32]

The aerosol characteristics have been shown to depend on the physicochemical properties of the drug solution. Bench studies have shown that same drugs with different fluid properties can have varying outputs from the nebulizer. A low output has been reported when a viscous solution is nebulized using a mesh nebulizer; this appears to be a consequence of apertures failing to produce a droplet with each oscillation. In one of the study, they compared two most common albuterol preparations used for nebulization:[1] Ventolin® (albuterol) respirator solution of which 2.5 mg (0.5 mL) is diluted with 2 mL of normal saline solution, and[2] the preservative-free, pre-diluted Ventolin® (albuterol) nebules PF (2.5 mg/2.5 mL), using two different jet nebulizers. Drug availability was greater with the albuterol respiratory solution, due to the surface activity of the preservative benzalkonium chloride. Differences in drug availability between nebulizers exceeded fourfold depending on the preparation, the nebulizer, and the nebulizing flow. Hence, drug formulation can impact the nebulizer output. These differences could not have been predicted from the manufacturer's specifications.[33]

In one of the studies, the effect of fluid physicochemical properties has been evaluated on the aerosols generated from VMN, using fluids having a range of viscosity, surface tension and ion concentration. Two nebulizers were investigated: the Omron MicroAir NE-U22® (passively vibrating) and the Aeroneb Pro® (actively vibrating) mesh nebulizers. Assessment of nebulization efficiency was done by total aerosol output, droplet volume median diameter (VMD), and fine particle fraction (FPF). Increased viscosity resulted in a decrease in VMD and an increase in FPF. It also resulted in prolonged nebulization and reduced output rate, particularly for the Omron nebulizer. Both nebulizers were unsuitable for delivery of viscous fluids since nebulization was intermittent or it completely ceased at >1.92cP. No clear effect of surface tension was observed on the performance of these nebulizers employing a vibrating-mesh technology. However, when viscosity was low, reduced surface tension seemed advantageous in shortening the nebulization time and increasing the output rate, but for the Omron nebulizer this also increased the droplet VMD and decreased the FPF. The study has shown that nebulization with VMN was highly dependent on fluid characteristics and nebulizer mechanism of operation.[34]

In another study the output and particle size distribution of several series of aqueous solutions were measured using the aeroneb micropump nebulizer (a VMN device). Aerosol output measurements were made gravimetrically, and the particle size distributions were obtained by laser diffractometry. For non-ionic solutes, addition of sodium chloride dramatically increased the output rate and decreased the droplet size at low solute concentrations. Increasing viscosity caused a significant decrease in output. Caesium chloride displayed increased output rate with concentration due to the rising density. Based on calculations with the number of apertures and oscillatory frequency, low output rates appeared to be a consequence of apertures failing to produce a droplet with each oscillation. Overall, ionic strength, density, surface tension, and viscosity affected the output rate in a manner that can be now empirically predicted.[35]

Evidence statement:

- Most of the nebulized drugs are available either in solution or suspension form. The drug dispersion in droplets generated may be more homogenous with solutions but not so with the suspensions.
- The ultrasound nebulizer is ineffective in nebulizing drugs which are in suspension forms (such as budesonide).
- The aerosol characteristics and nebulization efficiency have been shown to depend on the physico-chemical properties (viscosity, density, surface tension and ion concentration) of the drug solution and these effects are more pronounced with the use of mesh nebulizers.
- Mesh nebulizer is unable to perform optimally at high viscosity.

Recommendations:

- The drug dispersion in the aerosol generated on nebulization is more homogenous with solutions than suspensions (III A)
- The use of an ultrasound nebulizer is not recommended for the drugs in suspension form. (II A)
- Clinician and researchers should recognize that changes in the physico-chemical properties (viscosity, density, surface tension and ion concentration) of the drug solution may impact the nebulizer output and aerosol characteristics (III B)
- It is recommended to use the jet nebulizer if the viscosity of the solution is not known. Mesh nebulizers are not suitable for solutions with high viscosity (UPP)

Q8. What are the problems related to mixing various drug formulations in the nebulizer cup?

It is a common practice to mix nebulization solutions before administering it. Although not recommended, co-administration of drugs separately prescribed for nebulization is done in real life. Instead of cleaning, reassembling, and refilling the nebulizer to perform consecutive nebulization, it has been observed that at least 25% of patients attempt to save time by mixing the inhalation solutions/suspensions. This allows simultaneous administration of multiple drugs and reduces the total nebulization time. However, the impact of this practice on drug output and aerosol characteristics is poorly understood. Mixing of solutions can alter the physicochemical properties of the solution and consequently impact the nebulizer output also.[36,37] Incompatibility and/or instability of the medication mixtures can lead to impaired drug safety and/or reduced efficacy up to treatment failure. Further, simultaneous nebulization of inhalation solutions can affect drug delivery by altering the aerosol particle size and its distribution. Particle size needs to be 1 to 5 μm in diameter, since larger particles deposit in the upper airways and smaller particles may be exhaled. Hence, even if physicochemical compatibility of mixtures is proven, final recommendations for simultaneous inhalation cannot be made. Aero-dynamic characteristics of mixtures also need to be studied. Moreover, the clinical relevance of inhaling different drugs simultaneously and the differences in therapeutic outcome compared to consecutive inhalation should be investigated.[36,37]

In one of the studies, it was found that while nebulizing tobramycin (80 mg/2 mL) through two different jet nebulizers (Hudson 1720® & 1730®), using a flow rate of 6 and 8 L/min, addition of albuterol 0.5 mL (5 mg/mL) in one group in the nebulizer cup, lowered the surface tension of the solution and resulted in a greater output of larger respirable fraction of tobramycin as compared to the other group of tobramycin without albuterol. This effect was most apparent for the Hudson 1720® whereas the Hudson 1730® had a larger respirable fraction of tobramycin. Thus, different nebulizers, different nebulizer solutions, and different techniques of nebulization may result in quite different amounts of tobramycin aerosol output in the respirable fraction.[36]

The effect of drug admixtures (DA) on aerosol characteristics and drug output of nebulized albuterol delivered by a continuous output (CONT) and a breath enhanced nebulizer (BEN) was observed in one of the studies. Albuterol was nebulized alone (ALB) and combined with cromolyn sodium (A+CRO), ipratropium bromide (A+IB), tobramycin (A+TOB), flunisolide (A+FLU), and n-acetylcysteine (A+NAC). Albuterol output and aerosol characteristics were determined by impaction and chemical analysis. Lots of variations were seen in the aerosol MMAD; Geometric standard deviation (GSD); Respirable fraction (RF%); Respirable mass (RM) with different drug admixtures and with different machines. Hence, it was found out that co-nebulization of albuterol with other drugs can affect its output and aerosol characteristics and the type of nebulizer also has a definite impact on it. They concluded that in vivo data is needed to assess the clinical implications of our findings.[37]

In another study the compatibility, pH, and osmolality of N-acetylcysteine (NAC) nebulizing solution in the presence of ipratropium bromide or fenoterol hydrobromide were studied. Mixing ipratropium or fenoterol to NAC solution raised the pH and osmolality of the solution and a decline in the concentration of the three drugs after a passage of time. They found that NAC and ipratropium were stable in nebulizing solution within one hour of mixing whereas NAC and fenoterol were compatible for at least seven hours. Thus, it was concluded that mixing of drugs can alter the pH and final concentration of the drugs and the combination can lose potency if there is a delay in administering the mixed solution.[38]

A review by Kamin W. et al[39] presents a comprehensive overview of the available data concerning physico-chemical compatibility of commonly mixed nebulizer solutions and suspensions. Mixtures are designated as physically incompatible when colour or odour changed, and haze or precipitation occurred. The lack of physical incompatibility does not rule out chemical decomposition. Mixtures of inhalation medications can be designated as physicochemical compatible, when chemical stability (≤10% degradation) of each active substance is maintained with unchanged pH values, osmolality and physical appearance over a test period of ≤24 h. Potencies of antibiotics in inhalation mixtures are determined by fluorescence immunoassay (tobramycin) or by using the 'Microbiological assay of antibiotics' (agar diffusion assay). The information provided below in the table is based on their in vitro studies and a thorough literature search. Results indicate that many nebulizer solutions/suspensions are mixable without provoking incompatibilities. However, certain excipients contained in some of the tested drug products could be identified as a reason for incompatibilities, e.g. impaired activity of dornase alfa. Studies assessing the aerosol characteristics of compatible mixtures nebulized with commonly used nebulizers are limited and need to be

encouraged. The clinical efficacy of simultaneous inhalation of duplicate, tripartite or quadripartite mixtures must also be evaluated in clinical studies before final recommendations for the inhalation regimens can be made. The results for the compatibility of respective nebulized drug mixtures for the most used drugs in inhalation therapy are summarized in the Table 2[39-42].

Table 2 – Physico-chemical compatibility of commonly used drug solutions in nebulizers.

	Ipratropium	Albuterol	Levalbuterol	Budesonide	Fluticasone propionate	Cromolyn	NaCl solutions	Arformoterol	Formoterol	Acetylcysteine	Dornase alfa	Colistimethate	Tobramycin	Glycopyrronium
Ipratropium														NO DATA
Albuterol														NO DATA
Levalbuterol														NO DATA
Budesonide														
Fluticasone propionate														NO DATA
Cromolyn														NO DATA
NaCl solutions														NO DATA
Arformoterol														
Formoterol														
Acetylcysteine														NO DATA
Dornase alfa														NO DATA
Colistimethate														NO DATA
Tobramycin														NO DATA
Glycopyrronium	NO DATA	NO DATA	NO DATA		NO DATA	NO DATA	NO DATA			NO DATA	NO DATA	NO DATA	NO DATA	NO DATA

Compatible to mix
not recommended due to insufficient evidence
not compatible

Evidence statement:

- Mixing of drugs for convenience is a common practice, even if prescribed for separate administration. The physico-chemical compatibility of mixed nebulizer solutions and suspensions must be ensured before doing so.
- Mixtures of inhalation medications are designated as physicochemical compatible, when chemical stability (≤10% degradation) of each active substance is maintained with unchanged pH values, osmolality, and physical appearance over a test period of ≤24 h.
- Potencies of antibiotics in inhalation mixtures are determined by fluorescence immunoassay (tobramycin) or by using the 'Microbiological assay of antibiotics' (agar diffusion assay)
- Coadministration of different drugs can impact the aerosol characteristics and its output from a nebulizer. Incompatibility and/or instability of the medication mixtures can lead to impaired drug safety and/or reduced potency and efficacy up to treatment failure.
- Variations are seen in the aerosol MMAD; geometric standard deviation (GSD); respirable fraction (RF%); respirable mass (RM) with different drug admixtures and with different machines.
- The combination of the drugs may result in loss of potency if there is a delay in administering the solution.
- Many nebulizer drugs are mixable without provoking incompatibilities. However, even certain excipients used could be identified as a reason for incompatibilities, such as impaired activity of dornase alfa.
- Information has been provided in the table on compatibility of mixing drugs and this is based on their in vitro studies and a thorough literature search.
- Aero-dynamic characteristics after nebulization of mixtures also need to be studied. Such studies assessing these characteristics on compatible mixtures, nebulized with commonly used nebulizers, are limited and need to be encouraged.
- The clinical efficacy of simultaneous inhalation of duplicate, tripartite or quadripartite mixtures must be evaluated in clinical studies before final recommendations for the inhalation regimens can be made.

Recommendations:

- Mixing of drugs of various formulations in the nebulizer cup is recommended only to be done once the physicochemical compatibility of the combination is ensured. (III A)
- Mixtures that show change in colour or odour, or presence of haze and precipitation are designated as incompatible and should not be used. However, lack of physical incompatibility does not rule out chemical decomposition (III A)

- Only those mixtures are recommended to be used where chemical stability (≤10% degradation) of each substance has been shown and where pH value, osmolality; and physical characteristics are shown to be maintained over a period of ≤24 hours. (III A)
- Co administration of different drugs can impact the aerosol characteristics, nebulizer output, aerodynamic properties, stability, potency, and safety of the individual drugs. Hence, mixing of drugs is only to be done where these factors have been ascertained (III A)
- Excipients present in the drug formulation also need to be considered while combining drugs since these have also been identified as reasons for incompatibilities even if the active drug remains to be the same (III A)
- It is recommended to use freshly prepared mixtures of compatible drugs as delay in administration may result in loss of potency of constituent drugs (III A)
- Some preliminary recommendations, based on the literature available, on mixing of some of the drugs are given in the table, may be utilized for clinical purposes (UPP)
- It is recommended to carry out in vitro and clinical studies, which so far are limited, on compatible mixtures of 2 – 4 drugs, to find out their impact on the nebulizer output, aerosol characteristics, aerodynamic properties, and clinical efficacy of the drugs, before a final recommendation can be made. (UPP)

Q9. What are the different types of interfaces available for aerosol delivery to lungs during nebulization and how do they compare with each other?

In the present time there are multiple types of interfaces available for use with nebulizers for aerosol delivery including the mouthpiece, facemask, nasal mask, pacifier mask, high-flow nasal cannula and the hood. In an early study they compared the facemask and the mouthpiece for delivering nebulized albuterol to children having acute asthma. Their clinical evaluation and spirometry were performed at baseline and at 20, 40, and 60 minutes. It was seen that though there was no difference in the improvement in the two groups, the facemask group had a higher incidence of tremor. Mouthpiece was found to be as effective as the facemask but safer.[43] A retrospective analysis compared the efficacy of treatment between different interfaces and observed that adverse events were slightly higher in patients who received treatment with face masks (85%) than in those who received treatment with mouthpieces (78%).[44]

In a randomized trial, 18 asthmatic children were given albuterol through pneumatic nebulizer (Pari Boy®) at a flow rate of 3.5 l/min., using mouthpiece and facemask, in nine children each. Pulmonary functions were measured prior to inhalation therapy and again at 15 and 30 min after therapy. Patients using mouthpiece, 30 min after inhalation, had significant mean percent increases in FEV_1 and in FVC than those using a facemask.[45] An observational study in adults, comparing nasal vs mouth breathing during nebulization, reported that the penetration of aerosol to the lung was greatly reduced when breathing through the nose compared with mouth breathing.[46] A better drug delivery has been reported using the oral route in older children in another study. They found that for the nasal route, total lung deposition was lower in infants (while asleep) (median 1.3%, range 0.3-1.6%) than in older children (median 2.7%, range 1.6-4.4%).[47] A study was conducted using upper respiratory tract replicas representing infants/toddlers aged 5, 14 and 20 months and a breath simulator was connected to the replicas. It suggested that nasal breathing for aerosol delivery to the lower respiratory tract is similar to, or more efficient than mouth breathing (5 and14 months old); and the differences between nasal and oral delivery diminished with age. The drug delivery was equivalent in the 20-month model.[48]

There are multiple varieties of face masks available commercially (Dragon face, fish face, the standard nebulisation mask, valved mask). It has been seen that the type of mask design selected can have an impact on the inhaled drug delivery.[6,49] One of the studies showed that drug delivery was greatest with the mouthpiece and valved-mask with both jet and mesh nebulizers, while the standard aerosol mask was least efficient. In general, the delivery efficiency of jet nebulizer was less than mesh nebulizer.[6] In another study, three types of paediatric face masks: standard paediatric and two proprietary paediatric face masks– dragon and fish face and three different distances from the face for the mask were used: at 0 cm, 1 cm, and 2 cm. With all 3 masks there was a statistically significant difference ($p < 0.001$) in inhaled mass between the 0 cm and 2 cm distance. The fish mask had a significantly higher ($p < 0.001$) inhaled mass than the dragon mask or the standard mask, at all 3 distances.[49]

The selection of facemask can also influence facial and eye deposition of the nebulized drug. A study using seven commercially available facemasks showed that all facemasks leaked aerosol, with significant facial (0.44 - 2.34% of nebulizer charge) and eye deposition (0.09 - 1.78% of nebulizer charge).[50] The facemasks have also been divided as front loading and bottom loading. In the front-loaded masks, the nebulizer is inserted directly into the facemask in front of the mouth while in the bottom-loaded masks the aerosol enters the mask from below the mouth. Though front-loaded nebulizers are more effective, there is a greater deposition of the drug on the eyes and face.[50-52] While selecting facemasks, it is also important to ensure a proper fit and an adequate seal. Studies have shown that the use of a non-sealed facemask can drastically reduce the drug delivery during nebulization due to leaks around the face mask.[53-55] Ensuring a proper mask fitting is important for effective drug delivery.[49,56]

Care needs to be taken while nebulizing bronchodilators to ensure, as much as possible, that the deposition of aerosol does not occur on the face and eyes to prevent them from its adverse effects. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes. Multiple case reports have raised the concern of acute angle-closure glaucoma and pupillary dilatation due to ocular deposition of nebulised bronchodilators and this is especially relevant in patients with a history of glaucoma.[57-59]

Some clinicians, to minimize the loss of drug from the exhalation port of the facemask, have tried to partially occlude the holes of the mask. However, in a bench study evaluating this technique, it was seen that the occlusion of the holes in the large mask did not increase the amount of drug delivery.[60] Another technique that has been tried is using valved-masks. The valved-mask is a modification of the non-rebreathing oxygen mask with one-way valves on ports on both sides of the mask so that gas passes from the mask through the one-way valves on exhalation. In a bench study, it was shown that the drug delivery increased when using a valved mask.[6] Studies have also tried to evaluate the use of a nose clip while using a mouthpiece interface for using a nebulizer. It is believed the air entrainment through the nose may occur during inhalation with a mouthpiece and by using a nose clip, the inhalation will only be through the mouth allowing better drug delivery. Another explanation would be that obstructing the nose may simply increase the inspiratory drive by a reflex mechanism; thereby also increasing the drug delivered to the lungs. Though a study had reported that the aerosol delivery is increased when using a nose clip with a mouthpiece;[61] another study failed to show any statistically significant difference[62] Wearing a nose clip can be uncomfortable too. Careful pairing of the aerosol generator and interface is also particularly important during trans-nasal aerosol delivery.[63]

Evidence statement:

- Multiple types of interfaces are available for use with nebulizers including mouthpiece, facemask, nasal mask, pacifier mask, high-flow nasal cannula and the hood. The mouthpiece allows for efficient drug delivery to the lung as compared to the face mask.
- Face masks are often associated with leakage of aerosol leading to significant facial and eye deposition This risk is mitigated by using a mouthpiece and the incidence of adverse events including glaucoma while using bronchodilators are reduced.
- Multiple types of face masks are available commercially (Dragon face, fish face, standard nebulization mask, valved mask). The design characteristics of the mask can influence the drug delivery, with the fish mask having higher inhaled mass. The distance between the face and the mask does not make any difference.
- The front-loaded masks (aerosol enters the facemask in front of the mouth) are more efficient than the bottom-loaded masks (aerosol enters the facemask from below the mouth) but these may produce greater facial and ocular deposition.
- Loose application of the interface decreases the drug delivery from the nebulizer and leads to wastage of the drug.
- Wearing nose clips while using a mouthpiece, has shown variable results in terms of aerosol delivery to the lungs and can be uncomfortable too.
- The occlusion of the holes (exhalation port) of the face mask do not increase the amount of drug delivered.
- Using a valved mask increases the drug delivery to the lungs.

Recommendations:

- Mouthpiece is recommended as the preferred interface over face masks having improved drug delivery during nebulization therapy. The drug deposition on the face and eyes, which is significant with face masks, is also eliminated with its use (II A)
- Use of a mouthpiece as against a facemask is particularly recommended when high doses of anticholinergics are used to avoid risk of glaucoma or blurred vision. It is also to be preferred when inhaled steroids are to be administered (III B)
- The choice of the interface should also be based on the convenience to the patient. Acutely ill patients, infants and young children who find it difficult to use a mouthpiece may use a facemask (UPP)
- The design of face masks has an influence on drug delivery, however, the distance between the face and the mask does not make any difference. (III B)
- The front-loaded face masks are preferred in comparison to the bottom-loaded masks for better drug delivery, however, to minimize drug deposition on the face and eyes while using anticholinergic drugs., a bottom-loaded face mask is preferred. (III B)
- Wearing a nose clip with a mouthpiece is not recommended, being uncomfortable to the patient, and its role in improving the drug delivery is also uncertain. (III B)
- A proper fit and an adequate seal of the mask must always be ensured. The occlusion of the holes on the face mask does not improve drug delivery. However, use of a valved-mask is recommended for better drug delivery (III B)

Q10. What is the 'Blow by' technique of administering inhaled nebulized therapy and how useful is it?

The blow by technique refers to a method where the aerosol plume is directed towards the patient's face by placing a jet nebulizer at a distance from the child. This technique is commonly used as an alternative to a tightly fitting mask especially among crying and uncooperative children as blow by technique is easily tolerated by patients. However, bench studies have shown that this technique is wasteful and does not ensure effective drug delivery.[49,56] In one of this study on a paediatric model, they used two types of interfaces, standard paediatric aerosol face mask and a T-piece (oral interface) capped at one end, placed at one end at 0 cm, 1 cm, and 2 cm from the inhalation filter at the inlet of a paediatric test lung. Inhaled drug mass, aerosol particle size and fine-particle mass (particles < 4.7 mum) and fine-particle fraction as percent of total mass were measured. Inhaled drug mass was greater with T-piece than with a standard paediatric aerosol mask and a significant decrease with mask or T-piece was seen as the distance increased ($p < 0.01$).[56]

In the other study by Lin et al., on a paediatric model, using jet nebulizer and 3 types of paediatric face masks (paediatric, dragon and fish masks) placed at 0 cm (mask directly applied to the mannequin face), 1 cm, and 2 cm. The drug nebulized was a 3-mL unit dose of albuterol sulphate. It was seen that with all 3 masks there was a statistically significant difference ($p < 0.001$) in inhaled mass between the 0 cm and 2 cm distance. The fish mask had a significantly higher ($p < 0.001$) inhaled mass than the dragon mask or the standard mask, at all 3 distances. Thus, the inhaled mass of albuterol is significantly reduced when the mask is moved away from the face and hence, 'The Blow by' technique is wasteful.[49]

Evidence statement:

- The 'blow by' technique, used in uncooperative children, is directing the aerosol plume towards the patient's face while keeping the nebulizer away from the child.
- The blow by technique reduces efficacy as it does not ensure effective drug delivery and is mostly wasteful.

Recommendation:

- The use of the blow by technique is not recommended for use. (III A)

Q11. What are 'Pacifier masks', and how useful and efficient are they?

Aerosol therapy in infants may get compromised by their not accepting face masks due to the crying habits etc which leads to reduced aerosol deposition in the lungs. Since 'suckling' on a pacifier often calms the infants, a face mask that incorporates a pacifier should become more acceptable to them. However, since infants must breathe nasally while suckling, lung aerosol deposition may be reduced due to impaction in the nose. The aim of the following studies was to compare lung aerosol deposition while suckling on a pacifier, incorporated into a mask, versus lung deposition while inhaling from a conventional mask.

The pacifier mask is a modification of the paediatric face mask with the attachment of the infant's own pacifier. This allows the child to keep suckling the pacifier while the nebulization is being done. The design of the mask allows for an optimal seal and minimal dead space. In one of the study, masks were developed, according to the 3-dimensional anthropometric data from three clusters, "small," "medium," and "large", amongst children (1 month - 4 years), These masks follow facial contours and gently seal to the child's face, and thus may minimize aerosol leakage and dead space. These masks also enabled children, "suckling" on their own pacifier.[64] In another clinical study, the drug delivery with these 'pacifier masks' was found comparable to that in infants breathing quietly through a well-fitting conventional mask and this also allowed for prolonged nebulization time. Twelve infants <12 months old, who regularly used pacifiers participated in the study. It was found that the mean lung deposition (±SD) while suckling using a mask with an attached pacifier ($1.6 \pm 0.5\%$ in the right lung) was like that with a conventional mask ($1.7 \pm 0.9\%$, $p=0.81$).[65]

It is known that the lung deposition of aerosolized medications is reduced with nasal breathing as compared to oral breathing. It is also well understood that infants are preferential nose breathers for the first 12 - 18 months of life, probably due to closer proximity of the epiglottis to the soft palate. Hence, it is more likely that infants inhale aerosols through their nose regardless of the fact whether they have a pacifier in their mouth. It should also be well understood that the nose has the highest airflow, resistance, and turbulence in the respiratory system and it acts as an efficient air-conditioner, humidifier, and filter, with the potential to filter out aerosolized particles, besides the noxious particles, allergens, or pollutants, subsequently affecting the drug delivery to the airways. This still is an unexplored field and requires study in greater detail, whether inhaling aerosol through the nose would influence its efficacy amongst infants during nebulization.

Evidence statement:

- Face masks are often not accepted by infants due to their non-cooperative nature and crying habits leading to reduced aerosol deposition to the lungs.
- 'Suckling' on a pacifier mask often calms the infants, hence, a face mask incorporating a pacifier is more acceptable to them. This allows the child to keep suckling the pacifier while the nebulization is being done allowing prolonged nebulization time.

- Using a pacifier during aerosol treatment in infants makes it as efficient as treatment with conventional masks besides having the calming effect. The design of the mask also allows an optimal seal and minimal dead space.
- Infants are preferential nose breathers and with a pacifier in mouth they inhale aerosols through their nose only. This may affect the drug delivery to the lungs since nose has the highest airflow resistance and it also filters the particles effectively

Recommendations:

- The pacifier equipped masks are recommended to be used to deliver nebulized drugs to infants while they continue suckling making it more acceptable besides having aerosol deposition similar to a conventional mask. (III A)

Q12. Can nebulization be done through high flow nasal cannula (HFNC)?

Nasal route for the delivery of pulmonary aerosol medications is rarely considered; however, in specific instances, this route may be quite useful. The high flow nasal cannula system is commonly being used to deliver humidified oxygen at high flow in both paediatric and adult patients. The use of this system to deliver aerosolized medications has been assessed in various studies. It has been observed that aerosols can be efficiently delivered through a humidified high-flow nasal cannula system.[66-69]

In an in vitro study by Bhashyam et al. they tested adult, paediatric, and infant cannulas with and without an inhalation-only breathing simulator. The cannulas were driven by 3L/min oxygen flows and radioisotope techniques were used for dose quantification. Total cannula output and system losses were measured. The study showed that aerosols can be efficiently delivered through a humidified high-flow nasal cannula system. Ninety percent of the aerosol volume was in sizes smaller than 4.2 +/- 0.4 micron (adult) and 3.8 +/- 0.5 micron (pediatric). System losses were highest in the nebulizer-humidifier connectors, heated tube, and humidifier. Losses in the nebulizer were very low.[66]

Ari et al[67] in another study tried to quantify aerosol delivery with heliox and oxygen in a model of paediatric ventilation. Albuterol sulfate (2.5 mg/3 ml) was administered through a paediatric HFNC with oxygen (100%) and heliox (80/20% mixture) using a VMN. The percent inhaled dose (mean ± SD) was similar with heliox and oxygen at 3 L/min (11.41 ± 1.54 and 10.65 ± 0.51, respectively. However, at 6 L/min drug deposition was ≥ 2-fold greater with heliox (5.42 ± 0.54) than oxygen (1.95 ± 0.50; P = 0.01) but overall, it was lower than that obtained at 3 L/min. Thus using a pediatric model of HFNC, reducing delivered flow from 6 to 3 L/min increased drug delivery by more than two fold but eliminated the increase in inhaled drug efficiency associated with heliox.[63]

One of the studies was conducted to compare aerosol delivery via HFNC, bubble CPAP, and synchronized inspiratory positive airway pressure (SiPAP) in a model of a simulated spontaneously breathing preterm infant. Albuterol sulfate (2.5 mg/0.5 ml) was aerosolized with a mesh nebulizer at two positions -[1] proximal to the patient an[2] prior to the humidifier. They found that aerosol could be delivered via all three devices, however, increased deposition was seen on placement of the nebulizer prior to the humidifier with all devices ($P < 0.05$). It was also seen that HFNC had a better drug deposition.[68]

Another study has tried to quantify aerosol lung deposition when combined with nasal high flow (NHF) as compared with standard practice. Lung doses were measured scintigraphically after nebulization with jet and mesh nebulizer placed within a NHF circuit in a spontaneously breathing model representing a full-term newborn and a 9-month-old toddler. Mesh nebulization within an NHF circuit delivering up to 4 L/min gas is likely to be at least as effective as jet nebulization with a facemask in infants and toddlers.[69]

Perry et al investigated the in vitro inspired dose and particle size distribution of albuterol delivered by mesh nebulizer through the Vapotherm® (Stevensville, MD) humidified HFNC system. The amount of albuterol delivered through this system was lower than the amount expected for a clinical response for most flow rates and cannula size combinations. Further studies are needed before routine use of aerosolized albuterol through a Vapotherm HFNC system can be recommended.[70]

To conclude, aerosols can be efficiently delivered through a humidified HFNC system, however, the position of the nebulizer in the circuit, the adapter used and the size of the cannula can impact the drug delivery.[69,70]

Evidence statement:

- The high flow nasal cannula circuit (HFNC) allows effective aerosol drug delivery to the lungs.
- There was no benefit of using heliox (80/20% mixture of helium and oxygen) against oxygen in delivering aerosols to the lungs.
- The position of the nebulizer in the circuit, the adapter used, size of cannula, and the type of HFNC system may impact the delivery of drugs.
- Aerosol delivery can be done via HFNC, bubble CPAP, synchronized inspiratory positive airway pressure (SiPAP) and nasal high flow (NHF) devices. Placement of the nebulizer prior to the humidifier is a preferable position

Recommendations:

- The high flow nasal cannula (HFNC) circuit, when in use, in the emergency department and the intensive care unit, is recommended to be utilized for the nebulized therapy having high efficiency. (III B)

- Use of heliox during nebulization through HFNC does not provide any additional benefit. (III B)
- Various factors such as position of nebulizer in the circuit, adapter use, the size of cannula, and the type of HFNC system, influence the drug delivery. Placement of the nebulizer prior to the humidifier is a preferable position (III B)
- Besides HFNC aerosol delivery can also be effectively done via other devices such as bubble CPAP, synchronized inspiratory positive airway pressure (SiPAP) and nasal high flow (NHF). (III B)

Q13. How useful is the 'hood interface' for aerosol therapy amongst neonates and infants?

The hood interface consists of an enclosure that covers the head and neck of a neonate or small children to deliver aerosol to the lungs while isolating them from the ambient air. Using this technique minimizes the likelihood of infants agitate and cry. Studies have shown that the aerosol therapy by hood is as efficient as by mask and also provides a better therapeutic index.[71] In a prospective, open, randomised crossover clinical trial on 14 wheezy infants nebulized with 99mTc albuterol solution administered through a small volume nebulizer (SVN) using mask and hood as the interface. Mean total lung deposition was 2.6% with the hood and 2.4% with the mask ($p > 0.05$). Variability with the mask was greater than with the hood (coefficient of variation 54% v 39%). Thus, aerosol therapy by hood was found to be as efficient as by mask with a better therapeutic index and is much better tolerated by infants and preferred by parents. Hood nebulisation is a simple and patient friendly mode of aerosol therapy in wheezy infants.[71]

A randomized, double-blinded, controlled trial; on 49 hospitalized infants with viral bronchiolitis compared the utility of the hood versus face mask for delivery of inhaled medications. In summary, the aerosol delivery by hood was found to be as effective as by mask. According to parents, the tolerability of the hood is significantly better than that of a mask.[72]

Similarly, in another prospective, open, randomized, controlled crossover clinical trial in 10 infants with bronchopulmonary dysplasia (BPD) who were on inhaled beta-agonist bronchodilators and corticosteroids, were randomly assigned to receive their nebulized treatments either by a facemask, or by a hood for 2-3 days, and then crossover to receive the same treatments with the other technique for another 2-3 days. Nebulization of aerosolized medications in infants with BPD by hood was less time-consuming for caregivers and was much better tolerated by the infants while being at least as effective as the conventional facemask nebulization.[73]

Kim et al, did a study to evaluate the influence of the head direction and breathing mode on the hood drug delivery in a 7-month-old girl airway model. Three head directions, i.e., face up, face side, and sitting (face front), and two breathing modes, i.e., oro-nasal and nasal breathing, were studied. A maximum of 20% difference in inhalability is observed among the three head positions. The face-side position has less facial-ocular deposition than the face-up position, while still achieving similar lung delivery efficiency. Hence, the face-side position appears to be a better option than the face-up position for comfort and safety reasons. Nasal breathing gives about 17.8% lower lung deposition and about 65% higher facial-ocular deposition than the oro-nasal breathing.[74]

Amirav et. al., did a numerical investigation of a hood inhaler, aiming at the assessment of the amount of aerosol that reaches the eyes of the patient when administering medications with such a device. It was shown that under optimal working conditions (i.e., when the infant's head is aligned to the funnel) the percentage of aerosol reaching the eye zone is 0.48%. However, when the funnel is tilted toward the eyes this amount is predicted to be 4.7%. The results obtained in this study are in good agreement with available in vitro data and it can be concluded that using the hood for aerosol therapy results in minimal deposition at the infant's eye area.[75]

Evidence statement:

- The hood interface is an enclosure that covers the head and neck of a neonate or infant to deliver aerosol to the lungs while isolating them from the ambient air.
- The 'hood' is an effective interface for delivering aerosol therapy to neonates and infants and is as efficient as a facemask while having a better therapeutic index.
- The face-side position has less facial-ocular deposition than the face-up position, while still achieving similar lung delivery efficiency.
- The hood interface provides better tolerability and is less time consuming than a mask.

Recommendations:

- The 'hood interface' is recommended as an efficient and effective technique for administering aerosol therapy to neonates and infants with better tolerability and therapeutic index than face mask, besides taking lesser nebulization time. (II A)
- Preference be given to hood interface over other masks while administering aerosol therapy to neonates and infants (II B)
- 'Face-side' position in 'hood interface' is the preferred position than face-up position, having similar lung delivery with less facial-ocular deposition (II A)

Comparison of various interfaces

Comparison of various interfaces has been provided in Table 3 below mentioning their description, advantages, and disadvantages along with suggestions for the best use:[76]

Table 3 – Comparison of various interfaces and techniques.

Interface	Description	Advantages	Disadvantages	Suggestions for the best practice
Blow-by	A technique that directs aerosol plume towards the patient's face by placing a jet nebulizer within a distance from the child that ranges from 1 to 30 cm.	Easy to use. Comfortable and easy to tolerate by the patient. A mask-free aerosol delivery technique. Used with fussing, crying and uncooperative children.	Inefficient aerosol drug delivery to children - Drug delivery with blow-by is 50%-85% less than the facemask. Cannot be used with breath- actuated nebulizers and mesh nebulizers.	Inhalation therapy with blow-by is not efficient; therefore, its use is not recommended.
Mouthpiece	A cylindrical tube that extends between the lips so that aerosol can pass through the oropharynx to reach the lower respiratory tract.	Efficient method of inhalation therapy amongst children. Aerosol drug delivery with a mouthpiece is two-fold more than that with a face mask.	Children less than 3 yr of age cannot use a mouthpiece. An adequate consistent seal around the tube is needed during inhalation therapy.	The mouthpiece should not be used for children who are less than 3 yr old. When using a mouthpiece the child should be encouraged to keep it in their mouth during therapy. If a child cannot keep the mouthpiece in his mouth with an adequate seal during aerosol drug delivery, another interface should be used for inhalation therapy.
Facemask	An interface that covers the nose and mouth. It is kept in place through an elastic band that extends beyond the back of the head or neck.	Can be used in children of all years of age. Can be used with nebulizers and pMDIs to deliver aerosolized medications to neonates and children.	A good facemask seal is needed for optimum aerosol drug delivery. It is frequently associated with crying, intolerance and rejection of the mask Crying and leaks between face and mask decrease aerosol drug delivery to children.	Select a lightweight and flexible facemask with anatomic contours to increase tolerability among children during therapy. Choose a facemask with small dead space and have a good face-mask seal to increase delivery efficiency of inhalation therapy. Use another interface if the patient starts to fuss, and cry during aerosol drug delivery with a facemask.
Pacifier mask	A face mask with the attachment of the infant's own pacifier.	A new and innovative facemask design that eliminates fear, discomfort and cry with the standard facemask. A child-oriented drug delivery interface designed to achieve therapeutic lung deposition in children. Improves compliance to inhalation therapy in infants.	The nose may filter out some of the aerosol particles due to nasal breathing amongst infants further prompted by suckling of the pacifier, affecting efficacy of the aerosol therapy	May be a good option for neonates, infants, and children who fuss, cry and do not tolerate other interfaces used for aerosol drug delivery.
Nasal mask	An interface that covers the nose to allow aerosol to pass through the nasopharynx to reach the lower respiratory tract.	Easy to use Better tolerated than the facemask.	Aerosol delivery with the nasal mask is less than that with the standard facemask.	May be used to provide aerosol therapy to neonates and children where mouthpiece or facemasks cannot be used for anatomical or other reasons
High flow nasal cannula	A tubing with two small prongs that are inserted into the nares to allow aerosol to pass	Efficient delivery of aerosolized medications to neonates and children. Children	More information about the safety and efficacy of aerosol drug delivery through HFNC is	When using mesh nebulizers for aerosol drug delivery to neonates and children, place the nebulizer prior to the heated humidifier.

(*continued on next page*)

Table 3 – (*continued*)

Interface	Description	Advantages	Disadvantages	Suggestions for the best practice
	through the nasopharynx and reach the lower respiratory tract.	may tolerate HFNC better than the facemask.	needed. Cannot be used with pMDIs.	
Hood	An enclosure that covers the head and neck of a neonate or small children to deliver aerosol to the lungs while isolating them from ambient air.	A good option for aerosol delivery to children who cannot use a mouthpiece and tolerate the facemask. Likelihood of agitating infants and making them cry is low. Aerosol delivery with the hood is the same as the facemask. Parents prefer the hood over the mask.	Users may need additional training and practice to provide proper inhalation therapy with the hood More time and parts may be needed for the set-up.	Use the hood for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask Put the infant in the face-side position when using the hood for inhalation therapy because it has less facial-ocular deposition than face-up position

Adapted from reference [76].

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PART - 3: Maintenance of Nebulizer Equipment.

Q1. What are the components of various kinds of nebulization machines?

The components of various types of nebulizers are mentioned below:

Jet Nebulizer

The whole Jet Nebulizer systems include –

- Compressor with power cord
- Tubing
- Nebulizer cup
- Accessories like mask, mouthpiece, nasal cannula, holding chamber, filter etc.

There are four different types of the pneumatic jet nebulizers and these have been designed to minimize the aerosol loss occurring during exhalation into the environment:[1]

1. Jet nebulizer with reservoir tube

The regular jet nebulizer provides continuous aerosol during inhalation, exhalation or breath hold leading to waste of aerosol to ambient air when the patient is not inhaling thus having only 8-15% utilization of the drug. To decrease this loss and increase inhaled aerosol mass, a large bore tubing is attached to the expiratory limb for it to act as a reservoir for the aerosol that is wasted to get collected and utilized, improving the drug deposition.[2,3]

2. Jet nebulizer with collection bag

In these nebulizers a reservoir is attached to the expiratory limb allowing continuous filling of all the aerosol generated. The patient inhales aerosol from the reservoir through a one-way inspiratory valve and exhales to the atmosphere through an exhalation port between this inspiratory valve and the mouthpiece.[3,4]

3. Breath-enhanced jet nebulizer

It uses two one-way valves to prevent the loss of aerosol to the environment, so that when the patient inhales, the inspiratory valve opens and gas enters in through the nebulizer. Exhaled gas passes through an expiratory valve present in the mouthpiece.[1]

4. Breath-actuated jet nebulizer

These are designed to increase aerosol drug delivery by generating aerosol only during active inspiration, preventing loss of drug during the expiratory phase, improving the efficiency more than three times, but it increases the nebulization time.[3] It is available in following three forms:

- Manual breath actuated
- Mechanical breath actuated
- Microprocessor breath actuated

Nebulizer cups, mask, tubing, and other accessories require frequent replacement. The compressor and power cord are long-lasting.

Ultrasonic Nebulizers[1]

Ultrasonic nebulizers work on the principle of converting electrical energy to high-frequency vibrations using a transducer, and these vibrations are transferred to the surface of the drug solution, creating a standing wave that generates aerosol. Ultrasonic nebulizers are available as small or large volume nebulizers. The large-volume nebulizers are mainly used for delivering hypertonic saline for sputum induction. Whereas the small-volume ones are used for nebulizing solutions such as inhaled bronchodilators, however, these are not suitable to nebulize drugs in the form of suspensions. The ultrasonic nebulizers consist of the following parts:

- Mask or mouthpiece
- Medication chamber
- Baffle type cover
- Piezoelectric crystal

Mask. mouthpiece, medication chamber require frequent replacement

Mesh Nebulizers[1]

Mesh nebulizers work on the principle of vibrating a piezo element (~128 KHz) moving liquid formulations through a fine mesh to generate aerosol. These are very efficient and have minimal residual volume (0.1–0.5 mL). These are available in two forms: active vibrating or passive vibrating mesh nebulizers. Active vibrating mesh nebulizers have an aperture plate with 1,000–4,000 funnel-shaped holes vibrated by a piezo-ceramic element that surrounds the aperture plate. The passive mesh nebulizers utilize an ultrasonic horn to push fluid through the mesh.

These nebulizers are powered by electricity or battery and have the following components:

- It has a mask or mouthpiece to inhale aerosols.
- The diameter of the mesh or aperture determines the size of the particle generated.

Mask, mouthpiece, medication cup may require replacements.

Evidence statement:

- Details of different machines and the components of all the three types of nebulizers: jet, ultrasonic, and mesh, have been shown and the components requiring frequent replacements have been mentioned.
- The pneumatic jet nebulizer comes in four different designs; ultrasonic nebulizer as small and large volume; and mesh nebulizer in active or passive vibrating forms.
- The four different types of pneumatic jet nebulizer include: jet nebulizer with reservoir tube, jet nebulizer with collection bag, breath-enhanced jet nebulizer, and breath-actuated jet nebulizer (manual breath actuated, mechanical breath actuated and microprocessor breath actuated). These newer nebulizers are designed to minimize aerosol loss during exhalation.

Recommendations:

- It is recommended to increase awareness about different types of nebulizers and their components for its proper usage, performance and maintenance. Some of the components of these nebulizers need to be regularly replaced (UPP)
- Among the jet nebulizers, the newer designs are recommended for improved drug delivery and lesser contamination of the ambient air by reduction in wastage of the aerosol. (UPP)

Q 2. What are the steps in using the nebulizer?

Some of the important steps in using the nebulizer are described below:

Medicine preparation

- Do proper handwashing
- Ensure that the nebulized drug which is due to be administered is prescribed.
- Check the expiry date of the solution to be nebulized.
- Assemble the nebulizer and connect the tubing between the nebulizer and compressor.
- Unscrew the top of the nebulizer chamber and pour the prescribed drug solution into it. Do not exceed the volume recommended by the manufacturer
- Ensure the top is firmly reapplied and is not loose.
- While using multiple nebulized drugs, do not mix these unless indicated

Steps for Correct Use of Nebulizers

These have been described below under two separate categories:

Technique for use of Jet Nebulizers[1]:

- Explain the procedure to the patient.
- Assemble tubing, nebulizer cup, and mouthpiece (or mask) properly.
- Apply the mask or mouthpiece to the patient in the proper manner.
- Place medicine into the nebulizer cup.
- Ensure that the patient is in an upright position and comfortable.
- Place the compressor near to the patient, connect to the power source, and switch it on.
- Patients are asked to breathe normally with occasional deep breaths. It is important to explain to the patient to breathe through the mouth and not to talk during the procedure.
- Keep the nebulizer chamber vertical during treatment and and not spill dose by tilting the nebulizer chamber.
- Ask the patient to tap on the nebulizer chamber intermittently to prevent condensation of the aerosol.
- If the treatment has to be interrupted, turn off the unit to avoid waste.
- The compressor should be switched off when the 'misting' has stopped or when sputter occurs or until the end of nebulization.
- Leftover solution in the chamber should be discarded.
- Rinse the nebulizer with sterile or distilled water, allow it to air dry and place it in its package for storage.

Technique for use of Mesh and Ultrasonic Nebulizers[1]:

- Correctly assemble the nebulizer as per manufacturer's directions.
- Check proper functioning of the nebulizer before use.
- Pour the solution into the medication reservoir. Do not exceed the volume recommended by the manufacturer.
- Ensure that the patient is in an upright position and comfortable.

- Turn on the power.
- Hold the nebulizer in the position recommended by the manufacturer.
- Follow the instructions for the breathing technique that is recommended by the manufacturer for the mesh and ultrasonic nebulizers.
- Ask the patient to tap on the nebulizer chamber intermittently to prevent condensation of the aerosol.
- If the treatment has to be interrupted, turn off the unit to avoid waste.
- At the completion of the treatment, disassemble and clean as recommended by the manufacturer.
- When using a mesh nebulizer, do not touch the mesh during cleaning. This will damage the unit.
- Disinfect the nebulizer, once or twice a week, following the manufacturer's instructions.

Precautions

- Read and follow the manufacturer's instructions properly.
- Assemble equipment properly and ensure that all connections are secured tightly.
- Do not spill a dose by tilting the nebulizer.
- Keep the mouthpiece in mouth during nebulization.
- Breathe through the mouth and take slow and deep breaths.
- In the event of unit getting overheated, turn off the unit, wait until it cools down, and then restart the unit
- Residual solutions should be discarded after use.
- Patients with COPD should not be given nebulization driven by oxygen.
- Patients with acute asthma should have nebulizers driven by oxygen (usually 6-8 l/min).
- Patients should be educated and trained in their language for nebulization.
- Make sure that the nebulizer is cleaned and dried between uses.

Evidence statement:

- Instructions for the assembly and use of the equipment, filling up of the nebulizer chamber, and precautions to be taken, have been given in detail.

Recommendations:

- Recommended steps to assemble equipment, filling up of nebulizer chamber, correct use of nebulizer, and precautions required must be followed for proper aerosol therapy (UPP)
- Patients with acute asthma are recommended to be nebulized with oxygen driven equipment, whereas those with COPD by air driven equipment (UPP)

Q3: What steps are to be taken while storing a nebulizer?
Proper storage and maintenance of the nebulizer:

- The leftover solution in the nebulizer should be discarded completely.
- It is important to ensure that nebulizers are thoroughly cleaned and dried since bacteria grow in wet, moist places.
- Make sure that all parts have been cleaned and disinfected.
- Keep the nebulizer components in a bag
- Follow manufacturer's instructions for storage of equipment and its different parts.
- Single-use devices should not be used multiple times.
- Nebulizer devices require servicing and maintenance checks as per manufacturer's advice.
- Replace components requiring frequent changes

Evidence statement:

- Instructions for proper cleaning and storage of the equipment are mentioned.
- Servicing and maintenance checks need to be followed as per manufacturer's instructions.

Recommendations:

- Nebulizer is recommended to be thoroughly cleaned, dried, and disinfected before storage as per manufacturer's instructions (UPP)
- Manufacturer's instructions should be followed for proper servicing and maintenance checks of the equipment. Single-use devices should not be re-used. (UPP)

Q4. How to clean and disinfect the nebulizer and maintain infection control?

(Please also see the information given in Section - E (Chapter-5).

i) What is the rationale for cleaning and disinfecting?

As per the CDC guideline for disinfection and sterilization in healthcare facilities 2008, nebulizer is placed in the category of "Semi critical medical devices" and as such, infection prevention and control guidelines recommend that they should be properly cleaned, disinfected, rinsed with sterile water and air dried.[5,6] It is well known that nebulizers can be a potential source of infection to the patients both at home[7,8] and within the hospital. Contamination and colonization of nebulizers has been documented in patients with cystic fibrosis,[9-11] asthma,[12,13] and immunodeficiency.[14] In the hospital it has frequently been associated with nosocomial infections.[15-22] One of the studies has shown that 73% of nebulizers were contaminated with microorganisms and 30% had potentially pathogenic bacteria, and these latter are associated with an increased risk of causing exacerbation in COPD patients.[23]

It has also been seen that approximately 85% of patients with cystic fibrosis fail to disinfect their nebulizers at home.[24-26] Further, it has been shown that nebulizer performance may change with time due to improper cleaning, maintenance, and disinfection procedures.[27] Periodic disinfection and nebulizer replacement is highly recommended to minimize contamination.[1] Regular cleaning and disinfection practices are very important steps of the use of nebulizers. Cystic Fibrosis Foundation guidelines recommend nebulizer to be washed with soap and hot water after each treatment.[28] The CDC also recommends nebulizers to be cleaned, rinsed with sterile water, and air-dried between treatments.[29] Hospital staff and patients should be well educated and aware of the importance of cleaning and disinfection of equipment, as recommended by the manufacturer. Sometimes the adherence to the infection control practice can also be influenced by personal, socio-cultural, and psychological factors.[30]

- *Final Rinse:* The patient should use sterile water (not distilled or bottled) for the final rinse which is made by boiling tap water for five minutes.[1,28]
- *Drying and Maintenance:* Since bacteria grow in wet, moist places, nebulizers should be thoroughly dried and stored in a clean dry place between treatments.[1] Drying can be enhanced by attaching gas flow to the nebulizer for a short time after it is rinsed.[1]
- Nebulizers must be kept free from being contaminated by following the manufacturer's instructions for care and cleaning.[1]

Evidence statement:

- The CDC guideline for disinfection and sterilization in healthcare facilities, (2008), categorises nebulizer in "Semi critical medical devices" and recommends its proper cleaning, disinfection, rinsing, and air drying after each use.
- Nebulizers have been documented as a frequent and potential source of bacterial contamination and colonization and have been linked with nosocomial infections in the hospital.
- Proper rinsing and drying of the nebulizer after cleaning and disinfection is important before storage since bacteria grow in wet and moist places. The drying is enhanced by attaching gas flow after rinsing.
- The performance of the nebulizer may change in time, if not cleaned, maintained, and disinfected properly. The hospital staff and patients need to be made aware of the importance of these.

Recommendations:

- Proper cleaning and disinfection of nebulizers is recommended to be done after each use to prevent bacterial contamination and colonization leading to nosocomial infection. Instructions given by the manufacturer must always be incorporated. (UPP)
- It is also recommended that nebulizers should be thoroughly dried and stored in a clean dry place between treatments. (UPP)

ii) What are the methods available for cleaning?

Cleaning Instructions for the "Jet Nebulizer[1]

When cleaning after each use

- Wash hands before handling equipment.
- Disassemble parts after every nebulization.
- Remove the tubing and set it aside. The tubing should not be washed or rinsed, however, its outside can be wiped with alcohol.
- Rinse the nebulizer cup and mouthpiece with either sterile or distilled water.
- Shake off excess water.

- Air dry on an absorbent towel.
- Store the nebulizer cup in a zippered plastic bag.

When cleaning once or twice a week

- Wash hands before handling equipment.
- Disassemble parts for proper cleaning.
- Remove the tubing but it should not be washed or rinsed. Its outside can be wiped with alcohol.
- Wash nebulizer parts thoroughly in warm water with liquid dish soap.
- Disinfect the nebulizer, based on the manufacturer's recommendations, or else its parts can be soaked in one of the disinfectants (mentioned in the chart given below).
- Rinse parts with sterile or distilled water.
- Shake off excess water, run compressed gas or air for a few seconds, and place all parts on an absorbent towel and allow them to air dry completely.
- Reassemble the nebulizer and store in a clean, dry bag container.

Evidence statement:

- Proper cleaning, disinfection, and drying of the nebulizer is done after disassembling the parts and removing the tubing which is not washed
- Cleaning and disinfection are done after every use with sterile water, however, when done once or twice a week, the washing of parts is done with warm water and liquid soap. Final rinse is to be done with sterile water.
- Manufacturer's instructions must also be followed in the maintenance of the equipment.

Recommendations:

Cleaning of nebulizer after each use is recommended to be done using sterile or distilled water. When cleaning once or twice a week, use liquid soap for thorough washing and use sterile water for the final rinsing. Manufacturer's instructions must always be followed for dis-infection. (III B)

iii) What are the agents available for disinfection and what are the other disinfection methods?

Regular disinfection of nebulizers is recommended to reduce the chances of colonization of microorganisms and infection. Some of the methods for disinfection include the following and either can be used as per convenience.[1,6,7]

1.Soak the parts of the nebulizer in a solution of 1-part household bleach and 50-parts water for 3 minutes, or in 70% isopropyl alcohol for 5 minutes, or in 3% hydrogen peroxide for 30 minutes, or in 1-part distilled white vinegar in 3-parts hot water for 1 hour. ((not recommended for CF patients)
2.Boil or microwave the nebulizer parts for 5 minutes. (Final rinse step not required).
3.Wash in a dishwasher at a temperature of > 158°F or 70°C for 30 minutes.(Final rinse step not required)

(It is important that all solutions should be discarded after disinfection).

Manufacturer's guidelines for cleaning and disinfection must be followed to maintain integrity and functionality of the nebulizer device.

Evidence statement:

- Disinfection of nebulizer is done after each cleaning to reduce the chances of bacterial contamination.
- Various disinfectants used to sterilize the equipment include: 70% isopropyl alcohol (soaking for 5 min.); 3% hydrogen peroxide (soaking for 30 min.); boiling (5 min.); 1-part white vinegar in 3-parts hot water (soaking for 1 hour); solution of 1-part household bleach and 50-parts water (soaking for 3 min.)
- Nebulizer can also be disinfected by boiling or microwave heating for 5 minutes or by washing in a dishwasher (at a temperature of >158°F or 70°C) for 30 minutes.
- Follow manufacturer's guidelines for cleaning and disinfection to maintain integrity and proper functionality of the equipment.

Recommendations:

- Regular disinfection after cleaning of the nebulizer is recommended after each use to prevent bacterial contamination and colonization in the equipment. (UPP)

- Disinfectants recommended for soaking nebulizer include use of one of the following: 70% isopropyl alcohol for 5 min, 3% hydrogen peroxide for 30 min, white vinegar and hot water in 1:3 ratio for 60 min, household bleach in water in 1:50 ratio for 3 min. (III A)
- Disinfection is also recommended by simply boiling the nebulizer for 5 min. or by microwave heating for 5 min. or by washing in a dishwasher (at a temperature of >158°F or 70°C) for 30 min. (III A)
- Manufacturers guidelines for cleaning and disinfection must always be followed for proper functioning of the equipment.

iv) How frequently should the nebulizer be cleaned?

- Unclean and dirty nebulizers can become a source of colonization for microbes.
- In the home, nebulizers should be cleaned after every treatment.
- Dirt can be difficult to clean if allowed to dry and stay long so rinsing and washing the nebulizer immediately after each treatment can help in reducing the risk of infection.
- According to the Cystic Fibrosis Foundation guidelines, parts of aerosol generators should be washed with soap and hot water after each treatment.
- Care should be taken not to damage any parts of the aerosol generator.

Evidence statement:

- Unclean and dirty nebulizers become a source of infection through colonization of microbes in it.
- Dirt can be difficult to clean if allowed to dry and stay long if not cleaned on a regular basis.
- Ideally parts of nebulizer should be cleaned after every treatment to help reduce the risk of infection.
- Proper care be taken to avoid damage to the nebulizer parts during cleaning.

Recommendations:

- It is recommended to clean and disinfect the nebulizers after every use, not allowing the dirt to dry up and stay long, making it difficult to clean. Caution needs to be observed to be gentle while cleaning to avoid damage to the parts. (UPP)

V) Are there any specific instructions for the mesh and ultrasonic nebulizers?

- Mesh and ultrasonic nebulizers should be cleaned and disinfected based on the manufacturer's recommendations.[1]
- It is important to remember not to touch the mesh during the cleaning of mesh nebulizers to prevent any damage to the unit.[1]

Evidence statement:

- Vibrating mesh and ultrasonic nebulizers should be cleaned and disinfected according to the manufacturer's recommendations only.
- The mesh in the vibrating mesh nebulizers is not to be touched during cleaning to avoid damage to it leading to malfunctioning of the equipment.

Recommendations:

- It is recommended to follow manufacturer's instructions and recommendations for proper cleaning and disinfecting the vibrating mesh and ultrasonic nebulizers avoiding any damage to the equipment. (UPP)
- Avoid handling of the mesh in VMN to prevent malfunctioning of the equipment. (UPP)

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Section – II (Group - B): Nebulization therapy in obstructive airway diseases

Abbreviations

AE - Adverse event
AECOPD - Acute exacerbation of chronic obstructive pulmonary disease
AMT - Abbreviated mental test
ATS - American Thoracic Society
BDP - Beclomethasone dipropionate
BID - Bis in die (Twice a day)
BIS - Budesonide inhalation suspension
BMD - Bone mineral density
BPM - Breaths per minute
BTS - British Thoracic Society
BUD - Budesonide
CF - Cystic fibrosis
CO2 (CO_2) - Carbon dioxide

COPD - Chronic obstructive pulmonary disease
CVD - Cardiovascular disease
DPI - Dry powder inhalers
ED - Emergency department
ERS - European Respiratory Society
FEV_1 (FEV1) - Forced expiratory volume in one second
FF - Formoterol fumarate
FP - Fluticasone propionate
FLU - Flunisonide
FVC - Forced vital capacity
g - Gram(s)
GB - Glycopyrronium bromide
GBn - Glycopyrronium
GINA - Global Initiative for Asthma
GOLD - Global Initiative for Chronic Obstructive Lung Disease
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
h - Hour
H_2O - Water
HPA - Hypothalamic-pituitary-adrenal
HR - Heart rate
HRQOL - Health related Quality of life
ICU - Intensive care unit
ICS - Inhaled corticosteroids
L/min - Litres per minute
LABA - Long-acting inhaled β_2-agonists
LAMA - Long-acting muscarinic antagonists
MDI - Metered dose inhaler
mg - Milligram(s)
mg/mL - Milligram(s) per millilitre
$MgSO_4$ - Magnesium sulfate
mL (ml) - Millilitre(s)
MMT - Mini mental test
μ (μm) - Micron (Micrometre)
μg (microg) - Microgram
OAD - Obstructive airway diseases
OD - Once daily
PCO2 (PCO_2) - Partial pressure of carbon dioxide
PEF - Peak expiratory flow
PEFR - Peak expiratory flow rate
pH - Potential of hydrogen (hydrogen ion concentration in a solution)
pMDI - Pressurized metered dose inhaler
RCT - Randomized controlled trial
RR - Respiratory rate
SABA - Short acting β2 agonist
SAMA - Short acting antimuscarinic agents
SD - Standard deviation
SGRQ - St. George Respiratory Questionnaire
TEAE - Treatment emergent adverse events
TS - Nebulized terbutaline sulphate
USFDA - United Stated Food and Drug Administration
UPP - Universal practice point

Introduction

Globally millions of people are suffering from asthma and chronic obstructive pulmonary disease (COPD), and the prevalence in India is also too high. Whereas, the prevalence of asthma is on rise, the global burden of COPD is also projected to increase, due to the aging populations and the continued use of tobacco and exposure to biomass fuels, underscoring the need for more effective management of this disease.[1,2] Exacerbations frequently occur in these patients requiring aggressive

management, visits to the emergency department (ED) and sometimes admission to the hospital. These two conditions are responsible for a high mortality too.[3,4,5,6]

For patients suffering from the obstructive airway diseases (OAD), inhalation of aerosolized medications such as bronchodilators and corticosteroids remain to be the mainstay of therapy. Although inhalation therapy with hand-held inhalers is more common, nebulizers are also widely used. These are relatively easier to use with the benefits of requiring minimal inspiratory flow, hand-breath coordination, and manual dexterity, along with the advantage of administering drugs continuously and in larger doses, besides the output of visible aerosol mist, giving more confidence to the patient. It is especially more convenient to the elderly and pediatric patients with asthma or COPD who often find nebulized bronchodilators to be more effective than the drugs delivered by other hand-held aerosol delivery devices. Moreover, many of these COPD patients, as their age advances, develop such comorbidities, which make them dependent on nebulizers for their aerosol therapy.[7,8] However, nebulizers have their own drawbacks too, which include device preparation, filling the drug in the cup before each medication, time taken to drug administration, and maintenance of equipment, besides the loss of drug during each exhalation.

Drug substances commonly used for inhalation therapy in OAD, comprise bronchodilators and inhaled corticosteroids, besides some other drugs such as mucolytics. However, there are several issues which have so far not been properly addressed such as indications of nebulizer use; drugs, their dosages and combinations; adverse drug reactions etc., which have been discussed in this section.

Q1. What are the indications for use of nebulization therapy in obstructive airway disease?

Nebulization may be used in COPD and asthma in following situations.

I.Poor hand breath coordination: This can occur in the following situations
- Cognitive impairment or impairment of dexterity
- In patients with special needs or altered mental status
- Patient too sick and unable to perform the necessary manoeuvres required to use handheld devices

II.For continuous drug administration and giving large doses to control the symptoms

One of the commonest applications of nebulization therapy is delivery of bronchodilator drugs.[9] Considerable literature has shown that equal bronchodilator effects can be obtained by using metered-dose inhaler (MDI) with spacer or nebulizer in acute exacerbation of asthma and COPD.[10-16] However, educating and training the patient in use of inhalation device is of prime importance. The cornerstone for education is knowledgeable health care providers. It has been stated that management of chronic airway disease is 10% medication and 90% education.[17] The operation of the inhalation devices also requires a degree of dexterity and coordination. Allen & Prior, studied the competence thresholds for the use of inhalers in people with dementia and stated that elderly people with significant cognitive impairment are unable to learn to use a standard metered dose inhaler.[18] Also cognitive function is an important determinant of inhaler technique.[19-20] Studies have found that evaluation of mini mental state examination and hand strength are significantly associated with correct use of MDI. Gray et. al. studied the characteristics of predicting incorrect MDI technique in older subjects and concluded that hand strength and cognitive status are significant predictors of incorrect inhaler use[21] Allen & Ragab. studied the ability to learn inhaler technique in relation to cognitive scores and tests of praxis in old age and concluded that elderly patients who are unable to learn to use a MDI despite a normal Abbreviated Mental Test (AMT) score do have evidence of cognitive impairment on testing with the Mini Mental Test (MMT) or were dyspraxic.[19]

Also there is evidence supporting use of nebulizers whenever high doses of drugs are required.[22-24] These high doses, either through a continuous aerosol therapy or through a bolus dose, are often required for the rescue management of patients with severe bronchospastic disease who do not respond to conventional therapy. Olshaker et.al. administered nebulized albuterol in adult patients in the emergency department (ED) setting, and after comparing bolus therapy to continuous nebulization, found the latter to be associated with increased peak flow rate, decreased respiratory rate, heart rate, blood pressure, and clinical severity score.[25]

A meta-analysis, including six randomized trials of continuous versus intermittent beta-agonist aerosol therapy in the treatment of adult acute asthma, including a total of 393 adult patients, found that at the end of treatment, continuous nebulization was associated with a greater decrease in heart rate but there were no significant differences in pulmonary functions or in the rates of hospital admission. The two methods were believed to be equivalent.[26]

Peters (2007), summarizing the practice of continuous bronchodilator administration for acute bronchospasm, suggested it to be at least as effective as intermittent nebulizer treatments, and further suggested that it may be superior in patients with the more severe airflow limitation.[27]

Evidence statement:

- Nebulization therapy in obstructive airway diseases (OAD) is more useful in old age patients and in all other situations with cognitive impairment leading to poor hand breath coordination.
- Nebulization is also useful in acute conditions in OAD, requiring large doses of bronchodilators through continuous drug administration or through bolus therapy, to control the symptoms.

Recommendations:

- We recommend use of nebulization therapy in obstructive airway diseases (OAD) in patients unable to use handheld devices due to their altered physical or mental status; or have poor hand breath coordination. (III A)
- Nebulization therapy is also recommended in OAD with severe airflow limitation requiring high doses of bronchodilators for symptom control. (III A)

Q2. Whether continuous or intermittent frequency of drug delivery should be used during nebulization in severe airflow obstruction?

Most of the studies have shown equal efficacy of continuous and intermittent drug delivery during nebulization.[38-41] However some of the studies have shown additional benefit of continuous bronchodilator therapy in patients with severe airflow obstruction. Rudnitsky et. al., in a comparative study showed decreased admission rate in continuous therapy group in patients who had a peak expiratory flow rate (PEFR) of less than 200 at presentation.[42] Similarly, Lin et. al., in his study showed more improvement in the continuous therapy group in patients with FEV1 <50% predicted at presentation.[43] A systematic review and meta-analysis done by Rodrigo et. al. supported the equivalence of continuous and intermittent albuterol nebulization in the treatment of acute adult asthma.[44] In another systematic review by Camargo et. al., it was concluded that there was an overall decreased admission with continuous nebulization particularly in severe airway obstruction.[45]

Evidence statement:

- Continuous nebulization is more beneficial in patients with severe airflow obstruction and leads to decreased admission rate as compared to intermittent nebulization.

Recommendations:

- We recommend that preference should be given to continuous nebulization over intermittent in severe airflow obstruction, however, in cases with less severe obstruction, either of the two can be used. [II A]

Q3. What is the preferred driving gas for nebulization in patients of asthma and COPD?

It is a common practice that ambulances normally carry oxygen cylinders, but not compressed air. Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) with oxygen-driven nebulizer can result in hypercapnia and acidosis. Normally, both air or oxygen can be used as driving gas for nebulization in different clinical situations. Douglas et al conducted a study in hypoxemic patients with acute severe asthma and found that salbutamol nebulized in air produced only slight relief of airflow obstruction but there was no worsening of hypoxemia. No significant change in oxygen tension (PaO2) was observed at 15 or 60 minutes after administration of nebulized salbutamol.[28] Inwald et al conducted a review on oxygen treatment in acute asthma and concluded that beta2-agonist nebulized with oxygen should be the standard treatment for severe asthma attacks.[29] In a randomized crossover study, it was seen that using oxygen as the driving gas during nebulization had transient beneficial effects, however, oxygen needs to be continued after the nebulized salbutamol has been given.[30]

It is well known that administering high concentration oxygen therapy to patients with acute exacerbations of COPD may lead to carbon dioxide retention.[31,32,33] Attempts to avoid this have involved interrupted administration of oxygen. However, in a study by Gunawardena et. al. it was shown that when oxygen was used as the driving gas, patients with COPD without retention of CO2 showed no rise in PCO2 with oxygen against the common belief that its levels often rise, but those cases with initial CO2 retention did show a marginal rise in PCO2 which returned to baseline values shortly after stopping the nebulizer. Patients with asthma showed no rise in PCO2. When air was used as the driving gas none of the patients became significantly more hypoxic.[31]

In a prospective study by Heys et.al., done on 200 patients with AECOPD, it was found that the introduction of pre-hospital air nebulizers resulted in a reduction in oxygen therapy in these patients and a lower median pre-hospital oxygen saturation as well.[34] Edwards et al performed a randomized controlled trial to assess the effect on the arterial partial pressure of carbon dioxide ($PtCO_2$) of nebulized bronchodilator driven with oxygen versus air in stable severe COPD and found that nebulizers driven with oxygen resulted in significantly higher levels of $PtCO_2$ than those driven with air in these patients.[35]

Bardsley et. al. in a parallel group double-blind randomised controlled trial in 90 hospital in-patients with an AECOPD, compared the effects of air versus oxygen-driven bronchodilator nebulization on arterial carbon dioxide tension in exacerbations of COPD and concluded that oxygen-driven nebulization lead to an increase in $PtCO_2$ in exacerbations of COPD. They proposed that air-driven bronchodilator nebulization is preferable to oxygen-driven nebulization in AECOPD.[36]

The current BTS guidelines for oxygen use in adults in healthcare and emergency settings (section 10.4) recommend air-driven nebulization for patients with COPD and, if this is not available in the ambulance service, the maximum use of 6 min for an oxygen-driven nebulizer is to be done. This is based on the rationale that most of the nebulized medication will have been delivered during this period limiting the risk of hypercapnic respiratory failure.

Ambulance services are encouraged to explore the feasibility of introducing battery-powered, air-driven nebulisers or portable ultrasonic nebulisers.[37]

Evidence statement:

- Using oxygen as driving gas for nebulization in hypoxemic asthma exacerbations is more beneficial.
- Using oxygen in hypercapnic COPD exacerbations leads to further CO_2 retention.
- For nebulization during transportation of COPD patients, air-driven nebulizers are to be used, however, in their absence, oxygen-driven nebulizer can be used for a maximum of 6 minutes. Use of battery-powered nebulizers are to be preferred in the ambulance services.

Recommendations:

- We recommend using oxygen as the preferred driving gas for nebulization in hypoxemic patients with asthma exacerbations. (II A)
- Air as the preferred driving gas for nebulization is recommended in hypercapnic patients with COPD exacerbations. (I A)
- Air-driven nebulizers are recommended to be used by the ambulance staff in the treatment of patients of COPD during transportation, however, in their absence, oxygen-driven nebulizer can be used, but for a maximum period of 6 minutes. In the same case setting, oxygen-driven nebulizer should be used in patients with acute asthma. (III A)
- It is recommended that ambulance services should be encouraged to use battery-powered nebulizers. (UPP)

Q4. What are the drugs used for nebulization therapy in obstructive airway disease?
The groups of drugs for nebulization therapy in obstructive airway disease are as follows.[46-49]

1.***Corticosteroids:*** Inhaled corticosteroids (ICS) are used as the most effective controllers in the treatment of asthma and the only drugs that can effectively suppress the characteristic inflammation in asthmatic airways, even in very low doses. Inhaled corticosteroids have been shown to decrease severe exacerbations, hospitalization, and death. However, fear of unwanted local and systemic side effects remains a concern in patients using ICS, especially with high-dose regimens and long-term use[50] By contrast, ICS are largely ineffective in suppressing pulmonary inflammation in COPD and have a poor clinical effect. However, ICS may be useful during the exacerbations in these cases and in those having asthma COPD overlap. The ICS that have been used for nebulization are:

- Budesonide
- Fluticasone propionate
- Beclomethasone dipropionate (BDP)
- Flunisolide (FLU)

(Discussed separately in this section under Q. No.8 and 9).

2.***Bronchodilators:*** Although short-acting inhaled bronchodilators (SABA and SAMA) (e.g. levo-salbutamol or salbutamol and ipratropium) are still used as rescue therapy, the other important drugs used have been long-acting β_2-agonists (LABA), and long-acting muscarinic antagonists (LAMA).[51] These nebulized bronchodilator drugs are mentioned below:

β_2 agonists: The β_2 agonist used for nebulization are:

- Short acting β_2 agonist (SABA): Albuterol (Salbutamol), Levalbuterol (Levo-salbutamol)
- Long acting $\beta_2$agonist (LABA): Formoterol, arformoterol,

Antimuscarinics: The antimuscarinics used for nebulization are:

- Short acting antimuscarinic agents (SAMA): Ipratropium bromide
- Long acting antimuscarinic agents (LAMA): Glycopyrronium

(Discussed separately in this section under Q. No. 6 and 7)

3.***Other drugs:*** The other drugs for nebulization in obstructive airway diseases used in some specific situations are:

- Adrenaline (Epinephrine):

Adrenaline is a nonselective agonist of both α and β adrenergic receptors and was introduced into the treatment of asthma early in the last century.[52] It may have beneficial effects in asthma in addition to a direct β receptor mediated

bronchodilation, such as α receptor mediated reduction in microvascular leakage and oedema, and inhibition of bronchoconstrictor neural pathways.[53] In the past, adrenaline was considered as the first-line treatment for severe acute asthma and is still used when patients do not respond to standard treatment.[54,55]

Adrenaline has been used in the nebulized form also. A Randomized Controlled Trial (RCT) from India on 91 wheezing children concluded that nebulized adrenaline (0.1ml/kg/dose in 1 in 10,000 solution) is more effective than nebulized salbutamol (0.1mg/kg/dose) and is thus a better, inexpensive and relatively safe alternative available[56] Abroug et al in a study concluded that a single dose, nebulized adrenaline (2 mg), is as effective and safe as salbutamol (5 mg) in acute severe asthma with no side effects.[57] In a meta-analysis of 6 RCTs (1966-2005) including 161 adults and 121 children, comparing nebulized adrenaline and β_2 agonists, it was found that those on inhaled adrenaline showed a non-significant improvement in pulmonary function compared to patients getting inhaled β_2 agonists. Nebulized adrenaline >2 mg was found equivalent to 5 mg of salbutamol or terbutaline per dose, whereas <2 mg of adrenaline was inferior to 2.5 or 5 mg of salbutamol. No differences in heart rate and PaO2 were seen with the two doses of adrenaline No statistically significant difference in the benefit was seen between nebulized adrenaline and salbutamol in the cases of moderate to severe acute asthma.[54]

(Discussed in more details in Section-IV (Group- D)

- Magnesium sulphate

(Discussed separately in this section under Q. No. 10)

- Ambroxol/N-Acetyl Cysteine

(Discussed separately in Section IV (Group- D)

- Sodium Cromolyn: An inhaled anti-inflammatory agent for preventive management of asthma which acts by inhibiting sensitized mast cell degranulation preventing the release of mediators from mast cells. Because of their convenience, leukotriene receptor antagonists have largely replaced it as the non-corticosteroid treatment of choice. Moreover, nebulization solution of cromolyn sodium is not available in India

Evidence statement:·

- Various nebulized drugs used in obstructive airway diseases include corticosteroids, bronchodilators, and some other drugs.
- Inhaled corticosteroids in nebulized form include budesonide, fluticasone propionate, beclomethasone dipropionate and flunisolide.
- Inhaled nebulized bronchodilators include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (formoterol; arformoterol), SAMA (ipratropium bromide), and LAMA (glycopyrronium).
- Other drugs for nebulization in OAD include adrenaline, magnesium sulphate, ambroxol/N-Acetyl Cysteine and sodium cromolyn.

Recommendations:

- Bronchodilators in nebulized form are recommended to be used in obstructive airway diseases for the maintenance therapy or during exacerbations include beta-2 agonists: short acting (albuterol or salbutamol; levalbuterol or levo-salbutamol) and long acting (formoterol; arformoterol); and antimuscarinic agents: short acting (ipratropium bromide) and long acting (glycopyrronium) (UPP)
- Corticosteroids in nebulized forms recommended to be used in obstructive airway disease include budesonide, fluticasone propionate, beclomethasone dipropionate and flunisolide (UPP)
- Other nebulized drugs recommended to be used in non-responsive patients of obstructive airway diseases in certain special situations include adrenaline (epinephrine), magnesium sulphate, ambroxol/N-Acetyl cysteine, and sodium cromolyn. (UPP)

Q5. What classes of *bronchodilators, inhaled corticosteroids* and their combination formulations are available for nebulization in obstructive airway disease?

The nebulization solutions for OAD available in India include bronchodilators (β_2 agonist and antimuscarinic agents, both short and long acting), inhaled corticosteroids and some of their combination formulations.

1.The single agent drugs for nebulization in obstructive airway diseases available in India are as follows.[58,59]

Bronchodilators

- Albuterol (Salbutamol) (SABA)
- Levalbuterol (Levosalbutamol) (SABA)
- Formoterol (LABA)*
- Arformoterol (LABA)
- Ipratropium bromide (SAMA)
- Glycopyrronium (LAMA)

* *Not available in Indian market yet*

Inhaled Corticosteroids (ICS)

- Budesonide
- Fluticasone

2.The combination formulations of drugs for nebulization for OAD available in India are as follows.[58,59]

SABA + SAMA.

- Albuterol (Salbutamol) + ipratropium
- Levalbuterol (Levosalbutamol) + ipratropium

LABA + LAMA.

- Arformoterol + Glycopyrronium

SABA + ICS.

- Levalbuterol (Levosalbutamol) + Budesonide

LABA + ICS.

- Formoterol + Budesonide

3.Other drugs that are used in some cases in certain specific situations are given below:

Other drugs:

- Adrenaline (Epinephrine) *(Discussed separately in Section- IV, Group-D also)*
- Magnesium sulfate *(Discussed separately under Q. No. 10 in Section-II, Group-B)*
- Ambroxol/N-acetyl-cystein *(Discussed separately in Section- IV, Group- D)*
- Sodium cromolyn

Evidence statement:

- Single agent bronchodilators available in India for nebulization include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (arformoterol), SAMA (ipratropium bromide), and LAMA (glycopyrronium). Nebulized formoterol is not available in India.
- Single agent inhaled corticosteroids available in India for nebulization include budesonide and fluticasone propionate. Beclomethasone dipropionate and flunisolide are not available
- Combination bronchodilator formulations for nebulization available in India include SABA + SAMA (albuterol or salbutamol plus ipratropium; levalbuterol or levo-salbutamol plus ipratropium); and LABA + LAMA (Arformoterol + Glycopyrronium)
- Combination formulations of inhaled corticosteroids and bronchodilators available for nebulization in India include SABA + ICS (levalbuterol or levosalbutamol plus budesonide); and LABA + ICS (formoterol + budesonide)
- Other drugs available as single agents for nebulization in India include adrenaline (epinephrine), magnesium sulfate and ambroxol/N-acetyl-cystein. Sodium Cromolyn is not available now.

Recommendations:

- Bronchodilator drugs recommended to be used in obstructive airway disease, available in India in nebulized form as a single agent, include SABA (albuterol or salbutamol; levalbuterol or levo-salbutamol), LABA (Arformoterol), SAMA (Ipratropium bromide), and LAMA (Glycopyrronium). Formoterol as a single agent in nebulized form is not available (UPP)
- Corticosteroids recommended to be used in obstructive airway disease, available in India in nebulized form as a single agent, include budesonide and fluticasone propionate (UPP)
- Bronchodilator drug combinations recommended to be used in obstructive airway disease, available in India in nebulized form, include SABA + SAMA (albuterol or salbutamol plus ipratropium; levalbuterol or levosalbutamol plus ipratropium); and LABA + LAMA (Arformoterol + Glycopyrronium) (UPP)
- Combination formulations of inhaled corticosteroids and bronchodilators recommended to be used in obstructive airway disease, available in India in nebulized form, include SABA plus ICS (levalbuterol or levosalbutamol plus budesonide); and LABA + ICS (formoterol + budesonide) (UPP)
- Other drugs recommended to be used in obstructive airway disease for nebulization in certain special situations include adrenaline (epinephrine), magnesium sulfate and ambroxol/N-acetyl-cysteine. (UPP)

Q6. How to select appropriate bronchodilators, single or in combination, in patients of asthma and COPD?

Bronchodilator use in cases of asthma and COPD has been dealt separately under two separate heads:

Bronchodilators use in bronchial asthma:

Asthma is one of the chronic respiratory disorders that has repeated episodes of exacerbations which may sometimes lead to hospital or ICU admission often requiring nebulization with bronchodilators. A total of 18 randomized controlled trials (RCT) on nebulized SABA with SAMA versus SABA alone, showed that there is no extra benefit with combination therapy in 11 trials, while 7 studies showed extra benefit with combination therapy.[60-77] The most used SABA in 14 of these studies was albuterol (salbutamol), while ipratropium was the most common SAMA in the equal number of studies. In a Cochrane systematic review of 23 studies, including 2724 participants, showed that combination therapy was effective in reducing hospitalizations compared to SABA alone, particularly in severe exacerbations[78] Rodrigo et al. in a systematic review with meta-analysis of 16 RCT in adults asthma showed significant reduction in hospital admission and greater increase in spirometric parameters with combination therapy versus single therapy[79] Global Initiative for Asthma (GINA) 2017 has advised for nebulized SABA for severe acute exacerbation in ED[80] Indian guideline for asthma 2015 recommended nebulized SABA/SAMA for asthma patients, who are not able to use MDI with spacer.[81] British guidelines on the management of asthma 2016 recommended for nebulized SABA with or without SAMA by continuous oxygen for acute severe or life-threatening asthma.[82]

Levalbuterol (Levosalbutamol), a refined form of albuterol, also a SABA is used in the treatment of asthma and COPD. There are studies comparing it with albuterol which find it to be more efficacious and safer, having a higher potency. Clinical studies, especially in children, have shown a similar bronchodilator response with levalbuterol as compared to racemic albuterol, even when administered at one-half or one-fourth the dose, both in long and short term treatment thus confirming a better therapeutic index.[83-88] Studies on outpatient asthma patients who were treated with levalbuterol showed a significantly greater increase in FEV1, a longer duration of action and fewer side effects.[89-91] Studies have shown that levalbuterol have better tolerability in terms of tachycardia and hypokalemia.[92] However, there are also studies which do not show that it works better than albuterol thus there may not be enough justification for prescribing it.[93]

Formoterol, a LABA, is used as an inhaled bronchodilator therapy for patients with asthma and in COPD, having a unique characteristic of rapid onset and sustained duration of action compared with some other bronchodilators. Moreover, besides the maintenance treatment, formoterol is also reported to be effective as an as-needed reliever therapy in these patients. Usually, SABA are the preferred drugs as the initial bronchodilator for acute asthma because of their rapid onset of action. However, due to the short duration of action they require frequent administration. Usefulness of formoterol in the management of acute attacks of asthma has well been recognized. Formoterol, besides having rapid onset and long duration of action, also has a favourable safety profile, hence, an ideal alternative to SABA in the management of acute asthma exacerbation by providing rapid bronchodilation and reducing the need for frequent administration. Onset of action of formoterol is similar to albuterol (1-3 min), and 80-90% of bronchodilation occurs by 5-10 min of inhalation. Duration of action is up to 12 h. Efficacy of formoterol has been shown in acute non-severe asthma, acute severe asthma, exercise induced bronchospasm, childhood asthma, and COPD.[94]

As-needed Formoterol because of its rapid onset of action, can effectively relieve asthma symptoms on as needed basis. In a RCT, 50 acute asthmatic children (5-12 years old) were randomly assigned to two groups with 25 patients in each to receive either a nebulised single dose of two 12 microg FF capsules diluted in 2.5 ml of sterile saline solution; or 3 doses of albuterol every 20 min. for one hour at a dose of 0.15 mg/kg/dose, maximum dose 2.5 mg. Symptoms score, oxygen saturation and lung function testing were recorded before and one hour after commencing treatments. Single dose nebulised FF was found to be equivalent to three doses of albuterol in acute asthma in children.[95] Since budesonide/formoterol is available as maintenance and reliever therapy in Asia, formoterol is now being used as needed, but always with concomitant inhaled corticosteroids. Among patients with asthma in East Asia, as-needed formoterol and salbutamol had similar safety profiles but compared with salbutamol, formoterol reduced the risk of exacerbations, increased the time to first exacerbation and reduced the need for reliever medication.[96]

Arformoterol, a single enantiomer of formoterol, another selective, beta- 2 adrenergic agonist and long acting bronchodilator; acts in a way similar to formoterol, but perhaps having more potent bronchodilator properties. It is also now available as a solution for nebulization. Das et al. in their study on 50 patients with acute non-severe asthma have attempted to compare the efficacy and tolerability of arformoterol with albuterol nebulization. Patients were randomly assigned to two groups each with 25 patients, given albuterol (5mg) or arformoterol (15 μg), every 20 min. by nebulization in a double-blind manner. The PEFR was measured at the baseline and 5 min after each dose. Both albuterol and arformoterol were found to be equally effective and safe as a reliever medication.[94]

These LABA in long term management of persistent asthma are not to be used as a monotherapy but always in combination with controller therapy in the form of inhaled corticosteroids. Arun et al. compared the bronchodilatory effects of inhaled budesonide/formoterol (200μg and 12μg respectively) combination with budesonide (200μg)/albuterol (200μg) administered by MDI and spacer in children of 5-15 years with mild acute exacerbation of asthma in this double-blind, RCT. The primary outcome was FEV1% predicted in the two groups at 1, 5, 15, 30, 60 min after administration of the study drug. Albuterol or formoterol delivered along with ICS had similar bronchodilatory effects.[97]

(Note: More details on formoterol and arformoterol available under the COPD heading in this question. It is available as nebulization solution only in combination with budesonide in Indian market).

WARNING

The LABA have an increase in risk of asthma-related deaths and these carry a black-box warning of the USFDA. A statistically significant increase in combined asthma-related deaths or life-threatening experiences were seen in a study in the total population receiving salmeterol. The safety of LABA in asthmatics has not been established and are contraindicated in them without use of a long-term asthma control medication.[98]

Evidence statement:

- Nebulization with a combination of SABA and SAMA compared with SABA monotherapy has no extra benefit in asthma except in patients with severe airflow obstruction.
- Nebulized levalbuterol is more potent than albuterol and shows a similar bronchodilator response as compared to albuterol even when administered at one-half or one-fourth the dose.
- Arformoterol and formoterol in nebulized form have potent and rapid bronchodilator effects with the benefit of a prolonged duration of action. Arformoterol is a single enantiomer of formoterol and is more potent than it.
- LABA or SABA in combination with inhaled corticosteroids (Levalbuterol with Budesonide; Formoterol with Budesonide) in nebulized form can be used in cases of persistent asthma.
- All the nebulized SABA (albuterol and levalbuterol) with or without SAMA (Ipratropium bromide) and LABA (formoterol and arformoterol) available singly (arformoterol) or in combination with LAMA (Arformoterol with Glycopyrronium) or ICS (Formoterol with Budesonide) can be used as a rescue medication too during exacerbations in cases of asthma. (Formoterol in India is available only in combination with budesonide)
- Single dose nebulised formoterol fumarate (12 microg) was found to be equivalent to three doses of albuterol (3 doses of 0.15 mg/kg to a maximum of 2.5 mg. every 20 min. for one hour) in acute asthma in children. As needed formoterol and albuterol have similar safety profiles but compared with albuterol, formoterol reduced the risk of exacerbations, increased the time to first exacerbation and reduced the need for reliever medication.
- All the beta agonists carry a black box warning of the USFDA (United States Food & Drug Administration) and should not be used without controller medication (Inhaled corticosteroids) in the management of chronic persistent asthma due to risk of asthma related deaths.

Recommendations:

- Short acting inhaled beta-2 agonists (SABA) are recommended as bronchodilators of choice for nebulization in acute exacerbation of asthma. (I A)
- Combination therapy of short acting beta-2 agonists (SABA) plus short acting muscarinic antagonist (SAMA) via nebulization is recommended as a better option than SABA alone in moderate to severe exacerbation of asthma. (I A)
- Levalbuterol is recommended as a more potent bronchodilator than albuterol, producing the same bronchodilator effect in half the doses, however, it is more expensive (I A)
- Nebulized forms of formoterol and arformoterol are recommended as a maintenance therapy in asthma in combination with nebulized corticosteroids. These have a rapid onset of action and are potent bronchodilators too with a convenient BID dosage schedule. Nebulized SABA with inhaled corticosteroids can also be used for this purpose but has an inconvenient dosing schedule. (I A)

- Nebulized LABA are also recommended as a preferred rescue medication over albuterol during acute exacerbations of asthma as these are equally effective to it in a single dose with a prolonged effect as compared to multiple doses of albuterol (3 doses every 20 min. for one hour). (II A)
- Further, use of LABA also reduced the risk of exacerbations, increased the time to first exacerbation and reduced the need for reliever medication. (II A)
- It is recommended not to use beta agonists without controller medication in the management of chronic persistent asthma due to risk of asthma related deaths. (III A)

Bronchodilator use in chronic obstructive pulmonary disease (COPD):

Short acting Beta-2 agonists and short acting antimuscarinic agents: Currently the inhaled drug therapy is the preferred route for managing cases of COPD and bronchodilators (β_2-agonists and antimuscarinics) are the mainstay of pharmacologic therapy in these patients. Long-acting agents are often used in moderate to severe patients to improve symptoms, exercise tolerance, and health-related quality of life (HRQOL) and reduce the risk of exacerbations.[96] Short acting beta agonists in combination with SAMA are also often used in such cases. The long-acting agents are indicated for maintenance treatment of COPD, while short-acting bronchodilators are used for rescue medication during acute exacerbations, or for use before physical activities to prevent the occurrence of symptoms. Some of the LABA (formoterol and arformoterol) are also suitable for rescue medication as they show a rapid onset of action with added benefit of prolonged action.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends nebulizers for specific sub-group of patients who are unable to use other inhalation devices, such as patients with exceptionally low inspiratory flow rates, where nebulizer treatment is more beneficial. Clinical trials have shown response in terms of significant improvement in FEV_1 and reduction in rescue medication use with nebulized bronchodilator therapy in cases of COPD. Five RCTs on nebulized SABA with SAMA versus SABA alone in COPD patients, showed no extra benefit with combination therapy versus either alone.[61,68,99-101] A Cochrane systematic review of 9 studies showed that combination of SABA and SAMA therapy in COPD did not increase FEV1 more than either drug alone.[102] In another Cochrane systematic review of 3 studies showed that $beta_2$-agonists and ipratropium both produce small improvements in FEV1 with no evidence for a synergistic effect.[103] Indian guidelines on COPD 2013, released jointly by Indian Chest Society and National College of Chest Physicians (India) recommended nebulized albuterol 2.5mg every 20 min during the initial 1 hour.[104] The GOLD guideline 2018 recommends nebulized SABA for acute exacerbation of COPD since nebulization may be an easier delivery method for sicker patients.[105]

The RCTs on comparing between levalbuterol and albuterol have generally not demonstrated any significant differences between the two in terms of efficacy, occurrence of adverse effects, or hospital admissions.[106] Levalbuterol may have some advantages over albuterol in patients with COPD admitted to the hospital, including shorter length of stay[107] but albuterol was found to be 3-fold less expensive than levalbuterol in one of the study.[106]

Formoterol and arformoterol: Formoterol, in COPD patients, differentiates from some other β_2-agonists by its rapid onset of bronchodilation within 5 minutes of administration. Nebulized formoterol fumarate (FF) significantly increased FEV_1 relative to placebo ($P<0.001$) when administered in these patients for 12 weeks and had similar efficacy and safety compared with the original FF dry powder formulation. Patients treated with nebulized FF reported greater treatment satisfaction and perception of disease control compared with treatment with short-acting bronchodilators delivered 4 times daily.[108-110]

In a randomized, double-blind, double-dummy trial, COPD subjects (n=351, mean FEV1=1.3 L, 44% predicted) received nebulized FF 20 μg or FF as DPI 12 μg, or placebo twice daily for 12 weeks. No significant differences in efficacy were observed between the two, nebulized verse DPI.[108]

A randomized, open-label, crossover trial was conducted at 16 centers in the US on COPD subjects (n=109, 52.8% predicted FEV1) who received nebulized FF 20 mg BID or ipratropium and albuterol combined in a MDI QID for 2 weeks. After a 1-week washout, subjects were crossed over to the other treatment. Following a 2-week treatment period, twice-daily nebulized FF was significantly more effective in improving lung function than the ipratropium and albuterol combination MDI delivered four times daily.[110]

Furthermore, nebulized FF significantly increased bronchodilation in patients receiving LAMA, tiotropium bromide[111] which indicates that formoterol can improve lung function in combination with antimuscarinics. About tachyphylaxis to the bronchodilator effect of formoterol, it was not observed for 6 weeks when given as add-on treatment in patients receiving tiotropium maintenance therapy.[112-113] This finding was consistent with 12-week trials that did not show any tolerance to the effect of formoterol alone in patients with COPD.[108]

Tashkin et. al. in a study, in subjects of diagnosed COPD who were randomized to receive nebulized 20 μg FF inhalation solution twice daily plus tiotropium or nebulized placebo twice daily plus tiotropium for 6 weeks. Nebulized FF in combination with tiotropium provided statistically and clinically significant improvements in bronchodilation and symptom control over tiotropium alone and demonstrated good tolerability.[113]

Nebulization solution of combination of formoterol and budesonide is already available, and Triple drug fixed dose combination comprising of glycopyrronium pyrolate/formoterol and budesonide in a MDI, formulated with co-suspension delivery technology, as a maintenance therapy has undergone trials for the patients of COPD who need simultaneous use of inhaled corticosteroids.[114] It has already become available in India in a DPI form (with fluticasone in place of budesonide). Attempts for

lung deposition studies with these three drugs in a nebulized form are also being carried out utilizing Anderson Cascade impactor so that in future this form of triple drug therapy also becomes available for the treatment of COPD cases.[115]

Nebulized FF has been found to be safe for long term use. Sears and Radner analysed a primary dataset of 79 randomised controlled trials including 94 684 patients, 67 380 of whom were exposed to formoterol, while the complete dataset comprises 149 trials and 104 463 patients. They concluded that the dataset indicates no increased risk of asthma-related deaths among patients exposed to formoterol compared with non-LABA treatments,[116] *(Note: 'Formoterol' for nebulization is available in Indian market only in combination with budesonide)*.

Arformoterol is the (R,R) enantiomer of racemic formoterol. It is a potent, selective, beta- 2 adrenergic agonist and long acting bronchodilator; acts in a way similar to formoterol and salmeterol. It also acts similarly to inhaled rescue medications such as albuterol but maintains activity for 12 hours or more. Being a single enantiomer of formoterol, arformoterol may have hypothetically more potent bronchodilator properties, microgram per microgram, than racemic FF, but no major clinical differences between the two drugs have been observed in patients with COPD.[117] Maintenance therapy with nebulized arformoterol or formoterol demonstrated a 37% and 42% reduction in rescue albuterol use, respectively.[118]

A retrospective comparative study of the nebulized LABA, arformoterol, versus nebulized SABAs found that patients treated with arformoterol had significantly reduced odds of all-cause 30-day hospital readmissions relative to matched patients treated with SABAs.[119]

Arformoterol has been shown to improve lung function in combination with LAMAs. In patients with COPD who were receiving twice-daily nebulized arformoterol, tiotropium bromide given in combination produced significantly greater bronchodilation than either arformoterol or tiotropium monotherapies.[120]

In a multicenter, double-blind, RCT on 841 patients by Donohoe et. al. found,[121] patients receiving arformoterol or placebo had a similar incidence of AEs (72.9% vs 68.2%, respectively). Arformoterol has a low incidence of cardiovascular side effects with incidence of arrhythmia and ischemia like placebo. Arformoterol is safe in combination therapy with inhaled corticosteroids, tiotropium and rescue nebulization can potentially benefit patients with hyperinflation and low inspiratory flow rates.[122]

The economic burden of COPD is also substantial and these LABA have been found to be useful in reducing this burden. In a study among beneficiaries of Medicare with recent hospitalizations, exacerbations and COPD-related admissions increased the odds of receiving arformoterol ($p < .001$). Nebulized arformoterol treatment was more likely to be initiated in sicker patients with COPD.[123] In another study, nebulized arformoterol users had lower 30-day readmission rates, and fewer comorbidities than nebulized SABA users. In this population, maintenance treatment with arformoterol reduced costly COPD outcomes.[124]

Anti-muscarinics - So far use of nebulized muscarinic antagonists was limited to SAMA's (ipratropium bromide), while β-agonists are available both as SABAs (albuterol) and as LABA (FF, arformoterol tartrate) and hence to maintain an optimal bronchodilation coverage, three or four doses per day are needed when SAMA and SABA are delivered via a nebulizer which is time consuming and cumbersome making the compliance difficult. Due to their safety profile and to a better exacerbation-preventing effect compared to LABAs,[125-126] LAMAs are usually the preferred starting therapy for COPD patients, but nebulized form of LAMA so far was not available till glycopyrronium bromide (GB) was introduced recently. For maintenance bronchodilator monotherapy, LAMAs are preferred over LABAs, as LAMAs have demonstrated a reduction in exacerbation rate compared with LABAs.[127,128].

Phase II studies (GOLDEN 2 and GOLDEN 6) of nebulized glycopyrrolate (dose range 3–100 μg BID) demonstrated statistically significant and clinically relevant dose-dependent increases in FEV1, as well as an acceptable safety/tolerability profile over 4 weeks in subjects with moderate-to-severe COPD. The efficacy and safety findings supported selection of glycopyrrolate 25 and 50 μg BID doses for the Phase III GOLDEN studies and provided preliminary evidence for the use of nebulized glycopyrrolate as a maintenance therapy for COPD.[129,130]

Leaker et al in their study found single doses of nebulized glycopyrrolate ranging from 12.5 μg to 400 μg in 42 patients with moderate to severe COPD (GOLD II/III), to be well tolerated on being delivered by high efficiency nebulizer device and showed a rapid onset of bronchodilation with clinically meaningful improvements in lung function maintained over a 24 h period at all doses >50 μg.[131]

Phase III, GOLDEN-3 and GOLDEN-4, efficacy, and safety twin RCT's on COPD patients with moderate-to-very-severe COPD studied nebulized glycopyrronium (GBn), using mesh nebulizer for 12 weeks duration. To include a closer-to-real-life COPD population, patients with maintenance treatment with LABA therapy (31%) and ICS (29%) and co-existing cardiovascular disease (CVD) were not excluded in both studies. The administration of two doses of GBn (25 and 50 μg BID) resulted in statistically and clinically significant improvements compared to baseline in placebo-adjusted change in trough FEV_1 and FVC at *week* 12.[130,131] It produced a decrease in SGRQ total score in all subgroups. Mean baseline rescue medication use in GOLDEN 3 and 4 was similar across treatment groups (~3.0–3.5 puffs/day). There was no evidence of undesirable interactions with commonly used COPD medications (ICS, SABAs and SAMAs). Nebulized glycopyrrolate was generally well tolerated and with overall acceptable cardiac safety profiles in both trials.[132,133]

GOLDEN-5 study[134] long-term safety trial of 48 weeks of treatment with GBn, 50 μg BID, delivered via mesh nebulizer or tiotropium 18 μg OD, via dry powder inhaler (DPI) in 1,087 moderate-to-very-severe COPD patients with background use of LABA and ICS and history of significant CVD. Lung function results in the study confirmed the findings from GOLDEN-3 and

-4 studies. The overall treatment-emergent adverse events (TEAEs) were similar for glycopyrrolate and tiotropium groups throughout the study period.

Thus, nebulized glycopyrronium, a LAMA with the convenience of BID dose, may provide a better therapeutic alternative for COPD patients who have trouble operating hand-held devices and hence are not adequately treated and remain symptomatic. It is observed that more than half of COPD patients fail to use their handheld inhaler device correctly.[135] On the contrary, it is also estimated that several million patients regularly use standard nebulizers where treatment compliance may be suboptimal due to the long dose delivery times and lack of portability.

Evidence statement:

- Nebulization with combination of short acting beta agonist (SABA) and short acting muscarinic antagonist (SAMA) is not superior to either of them used alone in acute exacerbation of COPD.
- Nebulized levalbuterol may have some advantages over albuterol but clinically significant differences between the two in terms of efficacy, occurrence of adverse effects, or hospital admissions is not seen. Nebulized albuterol is much cheaper also as compared to levalbuterol.
- Nebulized formoterol (LABA) is useful as bronchodilator for regular maintenance therapy in COPD and as-needed reliever therapy due to its rapid onset of action. However, it is only available in combination with budesonide in India and not as monotherapy.
- Nebulized formoterol has a prolonged duration of action and hence in COPD patients it is used in BID dosage and these patients show greater treatment satisfaction response when compared with short-acting bronchodilators delivered four times daily.
- Nebulized Arformoterol, another potent, selective, long-acting bronchodilator; acts in a way similar to formoterol but is more potent. It can also be used as a rescue medication and is safe too.
- Maintenance therapy in COPD with nebulized arformoterol or formoterol, both show a reduction in use of rescue albuterol use, but more so with arformoterol.
- Maintenance therapy with arformoterol reduces costly outcomes of COPD such as readmission rates, greater COPD severity, and fewer comorbidities than nebulized SABA users.
- Nebulized glycopyrronium bromide (LAMA), available as maintenance therapy in moderate to very severe COPD cases, shows a rapid onset of action with significant improvement in lung function and reduction in exacerbation rate and is safe too. It can also be combined with LABA and inhaled corticosteroids.
- Nebulized formoterol and Arformoterol (LABA), both have a synergistic effect in cases of COPD when used in combination with tiotropium bromide (LAMA), given as a dry powder inhaler. Now, nebulized glycopyrronium bromide has also been combined with these drugs safely with better efficacy and convenient BID dosage.
- The new combination of Arformoterol with glycopyrronium for nebulization makes its use more convenient with superior bronchodilator effect.

Recommendations:

- Nebulized SABA or SAMA, both are recommended in acute exacerbation of COPD and are equally effective. Their combination is not superior to either of them used alone. (I A)
- Nebulized levalbuterol has no definite clinically significant advantage over albuterol and both are also recommended to be used for rescue medication during exacerbation in COPD. Levalbuterol is more expensive than albuterol. (II B)
- Nebulized formoterol and arformoterol, both are recommended in long term maintenance use and as rescue medication during exacerbation in COPD cases. Both are potent bronchodilators and have the ease of administration having a BID dosage schedule. Arformoterol is relatively more potent. (II A)
- Nebulized Glycopyrronium, a safe new long acting antimuscarinic antagonist, is recommended as a maintenance therapy in moderate to very severe cases of COPD. It can also be combined with LABA and inhaled corticosteroids (I A)
- The new Arformoterol (LABA) with glycopyrronium (LAMA) combination in nebulized form, is recommended in cases of COPD as a more efficacious and convenient combination for the maintenance therapy. (II A)

Q7. What are the dosages and side effects of nebulized bronchodilator drugs?

Albuterol and levalbuterol: In a total 15 RCTs on nebulized albuterol, the commonly used dose was 2.5 to 5mg in 11 studies.[60-68,71-75] The usual dose of ipratropium among these RCTs has been 0.5mg. in 12 studies[60,61,63-68,70-73,75-77] Nair et al in a study showed that there is no difference in outcome with 2.5mg versus 5mg albuterol nebulization in acute exacerbation of COPD.[136] British Thoracic Society (BTS) guidelines (1997) on nebulizer therapy recommended 2.5 to 5mg of albuterol every 4-6 hourly for acute exacerbation of COPD and bronchial asthma.[137] European Respiratory Society (ERS) guidelines for nebulization recommended albuterol in a dose 2.5 - 5mg and ipratropium in a dose of 0.5mg for acute exacerbation of asthma and COPD.[9] Whyte et al in a study concluded that 0.5mg of ipratropium is as effective as 1.0mg dosage in treatment of acute severe asthma.[138]

Thèse guidelines further state that additional benefit can also be obtained by adding anticholinergic treatment in acute asthma cases, however, no additional benefit has been demonstrated when anticholinergic therapy has been added to β-agonist therapy for AE COPD. It further advocates that the treatment may be repeated within a few minutes if there has been a suboptimal response to the first dose of nebulized treatment or continuous nebulized therapy may be administered until the patient is stable[3] Indian guidelines for COPD recommend albuterol in a dose of 2.5mg every 20 min for one hour.[104] Indian guidelines for bronchial asthma (2015) recommended the use of albuterol 2.5mg every 15 min. or > 4 nebulization per hour.[81]

American Thoracic Society (ATS) guidelines for the management of asthma exacerbations recommended albuterol in a dose of 2.5 - 5mg every 20 min for 3 doses, while the dosage of ipratropium used was 0.5mg every 20 min for 3 doses.[139] The use of short-acting anticholinergic bronchodilators is currently limited to management of acute severe asthma when used alone or in conjunction with short-acting beta2 -agonists in cases of AE COPD.

Benefits of adding intravenous albuterol to inhaled albuterol in children with acute severe asthma in the emergency department. with respect to shorter recovery time, are not well documented. A Cochrane review concluded that until more adequately powered, high quality clinical trials in this area are conducted it is not possible to form a robust evaluation of the addition of intra-venous beta2-agonists in children or adults with severe acute asthma.[140]

The nebulized SABA and SAMA are generally well tolerated with few local side effects. In a Cochrane systematic review of 23 studies on asthmatics, reported adverse events in 11 studies and showed that these are more in combination therapy than SABA alone. The common side effects were dry mouth, tremors, palpitation, anxiety, headache, nausea, blurred vision and agitation.[78] Brown et al. in another Cochrane systematic review of 3 studies showed that beta2-agonists and ipratropium in COPD patients had common side effects like dry mouth and tremor.[141]

The Common adverse events seen with beta2-agonists are tremors, palpitation, dry mouth, headache, anxiety and nervousness. The other less common ones are taste alteration, tachycardia, dizziness and hypokalaemia. The Common adverse events with anticholinergics are tremors, palpitation, dry mouth and headache; while less common ones are taste alteration, dizziness, anxiety, blurred vision and urinary retention.[3,78,137]

Nebulized albuterol and levalbuterol, both, are short-acting medications commonly used to treat acute episodes of bronchospasm and AE in patients with COPD.[142] Asmus and Hendeles concluded that levalbuterol offers no advantage over albuterol but is likely to be more costly.[143] Rahman et. al. stated that levalbuterol, in half the dose of albuterol, shows similar therapeutic effects in acute exacerbations of asthma. This study did not notice side effects such as tachycardia and hypokalaemia.[144] Earlier it was thought that levalbuterol might show lesser clinical side effects than the racemic albuterol but no difference in pulse rates and decrease in serum potassium levels was found in other studies, who thought it to be mediated mainly by the (R)-enantiomer.[145,146] Cockcroft et al[147] also reported that nebulized levalbuterol produced similar effects on heart rate as racemic albuterol, suggesting that tachycardia caused by albuterol is attributed to (R)-albuterol. Another study also reported that (R)- albuterol and racemic albuterol are equally effective in lowering serum potassium levels.[148] Thus, the bronchodilator effect and systemic side effects of albuterol reside with the (R)-enantiomer. Levalbuterol 0.63 mg is equipotent to albuterol 2.5 mg, and with a lower risk of adverse effects, except for the potassium-lowering effect.[149]

Formoterol fumarate (FF): This new LABA, is an effective bronchodilator mainly for the maintenance management of patients with asthma and COPD. However, it should not be used alone for asthma and must only be used with ICS (available only in combination with budesonide in India). In addition to its effectiveness as regular maintenance therapy, formoterol is also reported to be effective as an as-needed reliever therapy in these patients. Nelson et. al. (2007)[150] in a study on COPD population found no clinically significant cardiac effects with a twice daily treatment with nebulized FF inhalation solution (20 microg BID), compared to FF DPI (12 microg BID), or placebo, in a 12-week, double blind, RCT across 38 centers in United States.

Donohoe et. al. (2008)[151] in a double-blind study on moderate-to-severe COPD subjects found that nebulized FF (20μg BID) is well tolerated over long-term treatment and has a similar safety profile to the DPI formulation (12 μg BID). Results of safety monitoring for adverse events, laboratory values, and cardiac changes were similar between treatment groups, including serum potassium and glucose levels and no treatment-related increases in cardiac arrhythmias, heart rate, or QTc prolongation.

Another study in COPD patients found the safety profile of nebulized FF during 12-week and 1-year period to be like those of placebo and FF DPI formulations and it was concluded that maintenance use of nebulized FF is appropriate for patients with COPD who require or prefer a nebulizer for management of their disease. The most frequently reported adverse events were headache (5.7%), nausea (4.9%), diarrhoea (4.9%), COPD exacerbation (4.1%), dizziness (2.4%), and cough (1.6%). There were no deaths or drug-related serious AEs.[152]

Arformoterol: Now available as arformoterol tartrate (7.5 μg/ml in 2 ml respules), is a new addition to the basket of nebulization solutions. In a RCT including 841 patients of COPD, without excluding cardio-vascular disease, receiving nebulized arformoterol or placebo, did not find any significant difference between the treatment groups in terms of time to the first serious cardiac event.[121] The effect of arformoterol on the QT interval of 215 patients with COPD was studied in a randomized double-blind trial where arformoterol was given daily or twice daily (dose from 10 to 50μg) with no evidence of prolonging of cardiac depolarization.[153] Miles et. al. in their review have said that common to all LABA agents are potential side effects of stimulation at the beta-adrenergic receptor which include hypokalaemia, hyperglycaemia, anxiety,

nervousness, tremor, palpitations, and arrhythmias. They further said that effects on serum potassium and glucose concentrations are modest. Treatment-emergent arrhythmias were not significantly increased by arformoterol treatment, and serious cardiovascular events did not differ between placebo and treatment groups.[154]

A single-day study in adults of nebulized arformoterol, 15μg BID, compared with arformoterol 30 μg OD, in subjects with moderate to severe COPD, noted no serious adverse events[155] Another single-day study in paediatric subjects of consecutive doses of arformoterol 7.5 and 15μg found the medication to be well tolerated, with no clinically important changes in heart rate, blood pressure, or serum glucose levels.[156]

In a review Terasaki et al. found in general that when compared with formoterol and salmeterol, arformoterol had a similar rate of AE as expected from treatment with LABAs. However, it has been recommended that patients with comorbid conditions e.g. cardio-vascular diseases (CVD) and diabetes mellitus on long term use of nebulized drugs need to be periodically monitored with blood glucose and cardiac parameters.[157]

Four doses of arformoterol were tested for efficacy: 15μg BID, 25μg BID, 30μg OD and 50μg OD. Comparison of 15μg and 25μg arformoterol dosage showed greater improvement in FEV1 with the 25μg dose, but this dose had a 10% higher overall AE rate and 4% more myocardial ischemic events than the 15μg dose.[158]

Panettieri et al.[155] compared the efficacy of arformoterol 15μg BID to arformoterol 30μg once daily. The daily dosing had a 40% initial improvement of FEV1 area under the curve over the first 12 hrs but ultimately, the area under the curve of improvement in FEV1 over 24 h was similar between the two regimens.

Based on these trials, arformoterol 15μg twice daily was approved due to the optimal benefit of stable improvement in FEV1 and the least AE rate in this dose.

Glycopyrronium: Nebulized glycopyrronium (GBn) has been found to be safe and well tolerated in phase III randomized control trials, GOLDEN-3 and GOLDEN-4, which included COPD patients, who continued to take their maintenance treatment with LABA and ICS and were not screened out for co-existing CVD, and were given two dosages (25 and 50 μg BID). The pooled analysis of these trials demonstrated a combined overall incidence of Treatment Emergent Adverse Events (TEAEs) being numerically lower with GBn 25 and 50 μg BID doses compared to placebo (43.4, 50.7, and 52.3%, respectively). It also showed a very low incidence of anticholinergic-related events such as dry mouth, with an incidence ranging between 0.5 and 2.3% in patients treated with GBn; and the glaucoma-related adverse events were very rarely observed (0.5 and 0.2% for GBn 25 and 50 μg doses, respectively). As for urinary tract adverse events and urinary tract infection, these were reported in 2.3 and 1.9% for the GBn 25μg dose and 3.2 and 2.3% for the 50μg dose across the GOLDEN-3 and -4 trials, respectively. Urinary retention was not observed throughout these studies. In the GBn 25 μg BID and 50 μg BID treatment groups, the only TEAEs resulting in discontinuation occurring in more than 1 subject in total were worsening COPD (n = 2, 1 [0.5%] in each dose group) and cough (n = 2, 1 [0.5%] in each dose group).[132,133]

The GOLDEN-5 study, another Phase III, randomized controlled long-term safety trial studied the effects of 48 weeks of treatment with GBn, 50 μg BID or tiotropium 18 μg OD via DPI in COPD patients with background use of LABA and history of significant CVD. The primary endpoints were the incidence of TEAEs, Systemic Adverse Events (SAEs), and discontinuations due to TEAEs. Results from GOLDEN-5 trial, focused on long-term safety of GBn compared to placebo, showed that GBn BID was well tolerated, with a similar overall incidence of adverse events compared to the standard of care (48.6% for patients treated with GBn and 51.2% for tiotropium).[134]

Leaker et al found the drug to be well tolerated after single doses (from 12.5 μg to 400 μg) of nebulized glycopyrrolate in 42 patients with moderate to severe COPD (GOLD II/III) delivered by high efficiency nebulizer device.[131]

Evidence statements:

- Dose of albuterol is 2.5–5mg for each nebulization. The frequency of use is 2.5mg every 20 minutes for one hour and subsequently every 4-6 hours depending on the clinical response. For continuous nebulization albuterol is to be used at the dose of 5-10mg/hour for 3-4 hours depending on clinical response.
- Dose of levalbuterol is 0.63-1.25mg for each nebulization, half that of albuterol with a better/or equivalent bronchodilator effect.
- Dose of Ipratropium is 0.5mg for each nebulization. The frequency of use is 0.5mg every 20 minutes for 1 hour and subsequently every 4-6 hours depending on clinical response.
- Addition of intravenous albuterol to inhaled albuterol in acute severe asthma is of no added benefit.
- The Common adverse events with beta2-agonists are tremor, palpitations, dry mouth, headache, anxiety, and nervousness. Other less common ones are alteration in taste, tachycardia, dizziness, and hypokalaemia. Levalbuterol is relatively safe except for tachycardia and serum potassium level lowering effects.
- The common adverse events with anticholinergics are tremor, palpitations, dry mouth, and headache, while less common ones are alteration in taste, dizziness, anxiety, blurred vision and urinary retention.

- The dose of nebulized formoterol fumarate is 20 microg BID. It has been found to be safe for long term use. There are no changes in laboratory values including serum potassium and glucose; and treatment-related increases in cardiac arrhythmias, heart rate, or QTc prolongation.
- Nebulized arformoterol has been used in dosages from 30 to 50 microg in single or divided doses but 15 microg BID was found to be efficacious and safe. Its use is associated with a low incidence of cardiovascular side effects, having arrhythmia and ischemia similar to the placebo.
- Nebulized formoterol and arformoterol, both can be used during exacerbations in asthma and COPD in the same dosages due to their rapid onset of action. Both have a prolonged action up to 12 hours hence not requiring frequent dosages.
- Caution is required in cases of OAD with co-morbid conditions e.g. CVD and diabetes mellitus, while giving nebulized long acting beta2-agonists drugs, which may require periodical monitoring of blood glucose and cardiac parameters.
- Nebulized glycopyrronium has been used in dosages of 25 to 50 microg BID as a long-term maintenance therapy for moderate-to-very-severe COPD
- Nebulised glycopyrronium has been found to be safe and well tolerated with extremely low incidence of anticholinergic-related events and has been used safely even in the cases with cardio-vascular disease. Glaucoma-related adverse events are very rarely observed and urinary retention was not observed.

Recommendations:

- Recommended dosage of albuterol is 2.5 – 5 mg for each nebulization. In acute exacerbation of COPD and bronchial asthma, it is recommended in dosage of 2.5mg every 20 minutes for one hour and every 4-6 h subsequently depending on the clinical response. (I A)
- Recommended dosage of levalbuterol is 0.63-1.25mg for each nebulization, half that of albuterol. (I A)
- Recommended dosage of Ipratropium is 0.5mg for each nebulization. In acute exacerbation of COPD and bronchial asthma, nebulized ipratropium is given in dosage of 0.5mg every 20 minutes for one hour and every 4-6 hour subsequently depending on clinical response. (I A)
- The nebulized SABA and SAMA are well tolerated and safe with only few local or systemic side effects, more so with their combination therapy. Levalbuterol is relatively better tolerated than albuterol. However, caution is recommended in patients with morbid conditions e.g. cardiovascular diseases and diabetes etc. (I A)
- Recommended dosages of nebulized formoterol fumarate and arformoterol, for maintenance therapy in cases of asthma and COPD, are 20 microg BID and 15 microg BID respectively. (I A)
- Both, nebulized formoterol and arformoterol are safe on long term use with no serious adverse events including cardiovascular effects. However, it is recommended to have periodical monitoring of parameters in those having pre-existing CVD and diabetes mellitus, while using nebulized LABA. (I A)
- During acute exacerbations of asthma and COPD, use of formoterol or arformoterol in nebulized form is recommended in same dosages (I A)
- Recommended dosage of nebulized glycopyrronium (GBn), is 25 or 50 microg BID as a maintenance treatment for moderate-to-very-severe COPD (I A)
- Nebulised glycopyrronium (GBn) has been found to be safe and well tolerated with exceptionally low incidence of anticholinergic-related events and is recommended even in cases of COPD with cardio-vascular disease. (I A)

Q8. What nebulized corticosteroids and their combinations (ICS + SABA/LABA/LAMA) are available in India?
The nebulized corticosteroids and combinations available in India are shown in Table 1.[58]

Table 1 – Nebulized corticosteroids and its combinations with bronchodilators available in India.

DRUGS	DOSE
Budesonide	0.5mg. per unit[a]
	1.0 mg. per unit[a]
Fluticasone	0.5 mg. per unit[a]
	2.0 mg. per unit[a]
Budesonide + Levalbuterol (Levo-salbutamol)	0.5 mg.+1.25mg per unit[a]
Budesonide + Formoterol	0.5 mg + 20 mcg per unit[a]
	1.0 mg + 20 mcg per unit[a]

Budesonide and fluticasone are available as single agents in two different strengths and budesonide is also available as dual combination with levalbuterol (Levo-salbutamol) (single strength) and with formoterol (two strengths).
* Each 'unit' is 3ml. in volume.

Budesonide and fluticasone are available as single agents in two different strengths and budesonide is also available as dual combination with levalbuterol (Levo-salbutamol) (single strength) and with formoterol (two strengths).

Q9. What is the dosage, duration, frequency of use and side effects of treatment with nebulized corticosteroids in obstructive airway diseases?

Four inhaled corticosteroids are currently available for nebulization: budesonide (BUD), beclomethasone dipropionate (BDP), flunisolide (FLU), and fluticasone propionate (FP) of which BUD and FP are available in India. All these drugs are well known for their high affinity to the glucocorticoid receptor, good topical anti-inflammatory activity, and low tendency for systemic effects.[159-162]

Several large randomized controlled studies in subjects with chronic persistent asthma have demonstrated the efficacy and safety of budesonide inhalation suspension (BIS) at daily doses from 0.5 mg to 1 mg using a range of jet nebulizers. Some placebo-controlled studies also suggest that nebulized BDP, FLU, and FP, with some differences among them, are also clinically effective and safe.[163]

Mellon (1999) in his review article found BIS to be the first inhaled corticosteroid available for nebulization for infants and young children <4 years of age for the treatment of persistent asthma. The results of three randomized, placebo-controlled, double-blind studies demonstrated that BIS is effective and can easily be delivered to infants and children who lack the coordination and understanding necessary to use pressurized MDI with a spacer or inhalation-driven devices.[164]

In a 12-week, randomized study on children with moderate persistent asthma, four active treatment groups were formed: budesonide inhalation suspension (BIS) 0.25 mg OD, 0.25-mg BID, 0.5-mg BID, or 1-mg OD. Significant improvements in morning PEF were observed in all treatment groups, except for the 0.25-mg OD group, compared with placebo. All treatment groups showed numerical improvement in FEV1, but only the 0.5-mg BID dose was significantly different from placebo. Thus, BIS was found to be an effective and well tolerated therapeutic option for the cases of moderate persistent asthma in this age group who are not able to use other available delivery devices.[165]

Hvizdos & Jarvis[166] in a review of 3 multi-centre randomised, double-blind trials on infants and young children with persistent asthma, found that their day- and night-time symptom scores, and the need for rescue bronchodilators were significantly lower during treatment with BIS 0.5 to 2 mg/day than placebo. Amongst adults with persistent asthma, BIS < or =8 mg/day was compared with inhaled BUD 1.6 mg/day and FP 2 mg/day administered by MDI. Greater improvements in asthma control occurred in patients during treatment with nebulized BUD than with BUD via MDI, whereas FP produced greater increases in morning PEFR than nebulised budesonide. In several small studies they also found that nebulized BUD had an oral corticosteroid-sparing effect in adults with persistent asthma and that it may be as effective as oral corticosteroids during acute exacerbations of asthma or COPD. They recommended in infants and children aged 3 months to 12 years with asthma, a dosage of 0.5 mg to 1 mg of BIS going up to 2 mg/day, when starting treatment during an asthma exacerbation or during withdrawal of oral corticosteroids; maintenance doses are typically 50% lower than the starting dose. The recommendation for the starting dosage of BIS amongst adults and children, aged >12 years, was 2 to 4 mg/day, though higher doses may be necessary in very severe cases of asthma.[166]

Another study, extending to 12 weeks, partially blinded, randomized, on adolescents and adults (aged >or=12 years) having moderate to severe persistent asthma, having received ICSs previously by DPI or MDI, were given nebulized BIS 0.5 mg OD, 1.0 mg OD, 1.0 mg BID, or 2.0 mg BID, or budesonide DPI 400 microg BID (active reference arm). No difference in efficacy between BIS 2.0 mg BID and 0.5 mg OD was found when transitioned from ICSs delivered with a DPI or MDI. Subjects taking all BIS dosages experienced similar responses for variables associated with asthma control.[167]

Several studies, reviews and meta-analysis have compared dry powder form of FP to BUD and BDP among asthmatics and found FP to have more potency with better efficacy and safety ratio. A Cochrane review on randomised trials in children and adults compared FT to either BDP or BUD in the treatment of chronic asthma. Dose ratio 1:2: FP produced a significantly greater end of treatment FEV1 (0.04 litres (95% CI 0 to 0.07 litres), end of treatment and change in morning PEF, but not change in FEV1 or evening PEF. This applied to all drug doses, age groups, and delivery devices. FP led to fewer symptoms and less rescue medication use. Dose ratio 1:1: FP produced a statistically significant difference in morning PEF, evening PEF, and FEV1 over BDP or BUD. The effects on exacerbations were mixed. There were no significant differences in incidence of hoarseness, pharyngitis, candidiasis, or cough.[168]

Flic 12 study compared the effects of nebulized FP and nebulized BUD in 168 children with mild asthma exacerbation (aged 4-15 years) in addition to inhaled albuterol in a multicenter, randomized, single-blind, parallel group design. Children were randomly allocated to receive either nebulized FP (250 mcg) or nebulized BUD (500 mcg) twice daily for 10 days and they found that nebulized FP has the same effects as a double dose of nebulized BUD, when either drug is added to bronchodilator therapy. There was no evidence of hypothalamo - pituitary-adrenal axis suppression.[169]

Lin et. al. (2017) in a multicentre, randomized, active-controlled, single-blind, parallel-group 12-week study on 317 adult Chinese patients with severe persistent asthma compared FP inhalation solution (1.0 mg BID) to BIS (2.0 mg BID) via nebulizer, and found FP to be safe and efficacious leading to improvements in morning PEF and FEV1[170]).

Most studies amongst asthmatics have been done with ICS alone, however, some studies were performed in acute settings, mixing either BUD[171-175] or FP[176] with bronchodilators, through different nebulizer systems. Four of these studies

showed significant clinical efficacy when this admixture was compared to the placebo arm.[171,172,173,175] A study by Papi et. al. observed a significant improvement in symptom score and symptom free days in children with intermittent wheezing who received a co-admixture of BDP and albuterol.[177]

Further, the use of nebulized inhaled corticosteroids has also been correlated with reduction in relapses occurring in these cases. In an observational study among children (< or = 8 years), nebulized BUD treatment after an asthma-related emergency department visit/hospitalization was associated with a significantly reduced risk of recurrence compared with other asthma medications and with non-nebulized inhaled corticosteroids.[178]

Corticosteroids, especially the nebulized ones, have a limited role to play in cases of COPD. These could be useful to some extent either during the acute exacerbations of COPD or in those cases with overlap of asthma (ACOS) having eosinophilic instead of neutrophilic inflammation of mucosa. Systemic corticosteroids improve lung function, oxygenation, recovery time and hospitalization duration in acute exacerbations of COPD (AECOPD). Nebulized budesonide alone has also been found as a suitable alternative for treatment of COPD exacerbations in some patients.[179] Morice et al in a randomized control trial comparing nebulized budesonide with oral corticosteroids in AECOPD found that the clinical efficacy was similar in both groups, but adverse effects were less in the nebulization group.[180] Similar observations were made in other studies comparing oral corticosteroids with nebulized budesonide in AECOPD.[181-185] A review was done by Gaude and Nadagouda on nebulized corticosteroids in the management of AECOPD which concluded that nebulized BUD may be an alternative to parental/oral prednisolone in the treatment of these cases but further studies should be done to evaluate its long-term impact on clinical outcomes after an initial episode of COPD exacerbation.[184] Gaude and Nadagouda also conducted a longitudinal study in AECOPD and observed that nebulized BUD had similar range of improvement in spirometry variables as that in the parenteral steroid group. Also, it was observed that nebulized BUD reduced the duration of hospitalization and showed better improvement in HRQOL as compared to parenteral steroids.[185]

Only minor upper respiratory side effects are seen with use of nebulized corticosteroids. In a study by Murphy et al the side effects of nebulized budesonide were similar in the various doses used and also the most common adverse event was upper respiratory infection.[186] As per study done by Westbroek et al, nebulized fluticasone in two different doses daily was as well tolerated as placebo throughout the study. The most common adverse event reported was candidiasis of the mouth or throat.[187]

Zhimin Wu et.al. in a retrospective observational cohort study indicated that in infantile asthma nebulization with asthma under budesonide provided a longer post-treatment symptom-free duration and a lower risk of exacerbations than fluticasone.[188]

Most inhalers have greater efficiency than nebulizers for delivering ICSs. Nebulizers in general are a second choice, compared to hand-held inhalers, for delivering ICSs. Nebulized ICSs are prescribed to patients who are unwilling or unable to use inhalers, commonly amongst infants and in the elderly, where improper use of inhaler remains common in real life and is associated with poor disease control.[189-190]

High-dose regimens and long-term use of ICS may be associated with a variety of side effects, like those observed with systemic corticosteroid therapy. Unfortunately, systemic corticosteroids induce relevant adverse effects, even with short-term treatments.[191-192]The side effects to ICS may be local and systemic and the main local side effects are oral candidiasis, cough at time of inhalation, hoarse voice, and dysphonia.[193] The systemic side effects include suppression of hypothalamic-pituitary-adrenal (HPA) axis, impaired growth in children, osteoporosis, fractures, glaucoma, cataracts, and skin thinning. All these depend on several factors: delivery device used, the dose delivered, site of delivery, and individual differences in response to the corticosteroid[194] It is dependent on the amount of the drug absorbed into the systemic circulation which may occur through the gastro-intestinal tract after the fraction of ICS deposited in the oropharynx is swallowed or from the lungs after inhaling the drug.[50] The newer ICSs such as fluticasone, have a reduced systemic bioavailability from the gastro-intestinal tract but systemic absorption still occurs via the lung.

The most serious adverse effect of ICS is dose-related suppression of the HPA axis and even low-to-medium doses can affect basal cortisol secretion in children and adults[195-199] but whether this disturbance has any clinical significance remains unclear.[200] The effect of BUD at daily doses up to 2 mg on the HPA-axis was studied in 293 paediatric asthmatics (6 months to 8 years), for up to 52 weeks, without any clinically important difference, as compared to the conventional treatment group (where 35% were using ICSs via inhalers).[201] However, these high doses of BUD are seldom used in clinical practice. Hvizdos & Jarvis[166] in a review of 3 non-blind 52-week studies with BIS 0.5 to 1 mg/day found no effect on the growth velocity in children. Hypothalamic-pituitary-adrenal axis function was not affected by short (12 weeks) or long (52 weeks) term treatment with nebulised BUD.

Price et al[202] compared the effect of 7 days of nebulised FP with oral prednisolone on 24-h urinary-free cortisol excretion, systemic exposure, and safety. This was a randomised, double-blind, double-dummy, two-way crossover study including 31 children with stable asthma randomly assigned to nebulized FP (1mg bid) or oral once daily (2 mg/kg/day for 4 days (max 40mg) followed by half the original dose for 3 days (max 20mg). Nebulized FP had significantly less effect on HPA axis than oral prednisolone in asthmatic children in dosages used in AE of asthma. A significant dose-related adrenal suppression was observed in adult asthmatics with oral prednisolone at daily doses ranging from 5 to 20 mg, but not with BUD given at daily dosages ranging from 1 to 4 mg for 4 days.[203]

On the whole, nebulized BUD from adrenal suppression viewpoint seems to be safe and it occurs only occasionally at the highest doses after long-term regular treatment periods and perhaps in susceptible individuals.[204-205]

Growth retardation could be another side effect but short- and long-term studies suggest that patients who are treated with ICS may experience transient non-progressive decreases in growth velocity, but ultimately attain normal adult height[206-208] According to an Expert Panel Report ICS at the recommended doses are unlikely to cause effects on linear growth[209] Other studies also have reported similar results that no difference in growth of children was seen in children receiving nebulized BUD.[201,212] However, a meta-analysis of 16 RCT showed that ICS use for >12 months in children significantly reduced growth velocity at 1-year follow-up.[210] Another high-quality RCT showed a mean reduction of −1.20 cm in the final adult height with BUD versus placebo.[211]

The risk of osteoporosis and fracture, well known with oral corticosteroids, is not associated with the recommended doses of ICS.[206,213-214] A Cochrane review[215] concluded that there is no evidence of an effect of ICS at conventional doses given for 2–3 years on BMD or vertebral fracture. However, there is some evidence which points towards an overall risk which is dose dependent.[50]

The risk of pneumonia in COPD or asthmatic patients is another threat to the ICS therapy.[50] Meta-analysis and several recent case-control studies have demonstrated a significantly increased risk of serious pneumonia in these cases due to ICS therapy which shows a dose-response relationship.[216-219] A retrospective, observational study (ARCTIC), covering approximately 200,000 patients in Sweden, on analysis of the data from 6623 patients of COPD and/or asthma has shown a fourfold increased risk of pneumonia irrespective of ICS use than controls and the ICS use further increased the risk of pneumonia 5-fold among these patients. The highest risk was associated with the high dose of ICS and those with severe-to-very severe airflow limitation. ($FEV_1 < 50\%$).[220]

Other long-term effects of ICS, which too are dose related, could be a higher risk of cataract formation and glaucoma but the risk of the latter is likely exceedingly small.[221-223] Skin bruising and thinning especially in elderly patients may also be noticed.[224-229] BUD and BDP have also been used safely in pregnant women.[230-233] Post-marketing surveillance data also have confirmed the safety of nebulized ICSs across all ages.[234-235]

Adverse effects from ICSs need to be placed in context with their beneficial effects and the fact that, when used judiciously, the drugs prevent the need for courses of prednisolone. The dose must be tailored to the patient's needs and the dose may need to be reduced as lung function improves. High doses should be given only to patients who specifically require them.[236]

Nebulised corticosteroids have also been used in the management of acute asthma. In moderate acute asthma attack, nebulized FT (2000 mcg daily) was found to be as effective as systemic corticosteroid with regard to clinical improvement.[237-238] *Demirca et. al.*[237] studied the role of nebulized FP in acute asthma cases. In their randomized study on 81 children with moderate acute asthma attack, who were either given: nebulized FP (2000 mcg/day) or oral methylprednisolone (1 mg/kg/day). Nebulized FP was found to be as effective as the systemic route. Manjra et. al.[238] also reported similar findings comparing nebulized FP with oral prednisolone in children with an acute exacerbation of asthma. Advantage of nebulized FT has also been shown over systemic corticosteroids (intravenous methylprednisolone) in adult asthmatics managed in the ED following an acute attack.[239] However, children with severe acute asthma should be treated with oral prednisone and not with inhaled fluticasone or a similar inhaled corticosteroid. In a study increase in FEV_1, was significantly higher after 4 hours from the baseline and need for hospitalization significantly lower with oral prednisolone as compared with nebulized fluticasone.[240] Finally, the value of ICSs for the treatment of asthmatic and COPD exacerbations is promising,[241-245] but not fully evidence-based and cannot be recommended.

Evidence statement:

- Nebulized corticosteroids are used as a therapeutic option in most cases of persistent asthma and during its exacerbations, especially among infants, young children, and elderly people
- Whereas budesonide (BUD) and fluticasone propionate (FP) are the two inhaled corticosteroids commonly available for nebulization, budesonide has been used more often in the studies with extensive data available, whereas fluticasone propionate has not so often been used.
- Fluticasone propionate in dry powder form in half the daily dose has been found to have better efficacy compared to BUD and BDP in cases of persistent asthma but concerns about local side effects have been reported.
- The dosage of nebulized BUD among infants and children (3 months-12 years) with asthma is 0.5 mg to 1 mg/day, going up to 2 mg/day, when starting treatment, during asthma exacerbation or during withdrawal of oral corticosteroid. Amongst adults and children (>12 years), the dose is 2 to 4 mg/day, though still higher doses may be necessary in very severe cases of asthma. Maintenance doses are typically 50% lower than the starting dose.
- Nebulized FP (1.0 mg) compared to BUD (2.0 mg) in BID dose in severe persistent asthma in adults is equally efficacious and safe. Among children (4-15 years) with mild asthma exacerbation, nebulized BUD (500 mcg) or nebulized FP (250 mcg), BID was found to be equipotent.

- The dosage of nebulized FP is half that of nebulized BUD i. e. 0.25 to 1mg BID in cases of persistent asthma and this can be increased up to 2.0mg BID in severe obstruction.
- Combining nebulized BUD or FP with bronchodilators show significant clinical efficacy compared to the placebo arm.
- Use of nebulized corticosteroids has also been correlated with reduction in relapses occurring in cases with persistent asthma compared with other asthma medications.
- Nebulized BUD and FP in children and adults with persistent asthma, have an oral corticosteroid-sparing effect, reducing the hospital stay, improve lung function, improve quality of life, and prevent acute exacerbations. (preventing visits to ED and hospital admissions)
- Nebulized corticosteroids have limited usefulness amongst cases of COPD, where it may be of some use during acute exacerbations or in cases having overlap of asthma (ACOS) with eosinophilic inflammatory disease of airways.
- Nebulized corticosteroids have been found to be equally effective as compared to oral/parenteral corticosteroids during acute exacerbations of COPD and are safer too, but further studies are needed.
- Nebulized BUD and FP, when used judiciously, are safe having exceedingly few systemic adverse effect common with systemic steroids (suppression of HPA axis, impaired growth in children, osteoporosis, fractures, glaucoma, cataracts, skin thinning etc.) and that too are dose related. These may only be associated with some local adverse effects (oral candidiasis, cough at time of inhalation, hoarse voice, and dysphonia).
- Risk of pneumonia in COPD or asthmatic patients is a threat to the ICS therapy which shows a dose-response relationship.

Recommendations:

- Nebulized corticosteroids, in the form of BUD or FP are recommended for use as maintenance therapy in the cases of persistent asthma, unable to use other inhalation devices, especially the infants, young children and elderly people. It improves their lung function, QOL; prevents acute exacerbations, visits to ED and hospital admissions and reduction in hospital stay; and reduces risk of relapses in these cases. (I A).
- The recommended dose of nebulized BUD for infants and children aged 3 months to 12 years with persistent asthma is 0.25 mg to 0.5 mg BID going up to 1.0 mg BID during exacerbation. Starting dose in adults and children above 12 years is 1.0 to 2.0 mg BID, and still higher doses up to 4.0 mg BID can be given in very severe cases. The maintenance doses are 50% lower than the starting dose. Nebulized FP is more efficacious than nebulized BUD and is recommended in a dose ratio of 1:2 (I A)
- Nebulized BUD or FP in higher dosages have a promising role in the acute exacerbations of asthma or COPD, in place of systemic steroids, showing an oral corticosteroid-sparing effect, but their use is not recommended for want of fully evidence based studies. (I A)
- Nebulized BUD and FP are recommended to be combined with bronchodilators (LABA) for better efficacy in persistent asthma (I A)
- Nebulized FP and BUD are recommended for long term use and are safe too, if used judiciously, as no systemic adverse effects, commonly seen with the oral or parenteral corticosteroids, are seen. Only local side effects may be present. Risk of pneumonia in these cases remains to be a threat but it has a dose-response relationship (I A)

Q10. What is the role of nebulized magnesium sulphate in management of obstructive airway diseases?

Magnesium sulphate ($MgSO_4$) has been proposed as a possible additive treatment in acute asthma and has been shown to be effective in severe acute asthma when delivered by the intravenous route.[246] Clinical benefits of nebulized $MgSO_4$ have been studied with varying results. A few studies comparing albuterol with $MgSO_4$ showed that although $MgSO_4$ had a significant bronchodilator effect, albuterol was better than $MgSO_4$.[247-249] Studies comparing albuterol nebulization alone and albuterol plus $MgSO_4$ nebulization have shown different results. Some of the studies concluded that the combination enhanced the bronchodilator response.,[250-253] while others showed no additional benefit.[254-256]

A study by Talukdar et. al.[248] in cases of severe asthma compared nebulized $MgSO_4$ to nebulized albuterol and found that both agents led to improvements in PEFR and oxygenation but albuterol was found to be better than MgSO4. They had given four doses of 3 mL each of nebulized MgSO4 every 20 min (3.2% solution, 95 mg). Using nebulized MgSO4 in acute asthma Magnet et.al. found a significant bronchodilator effect of MgSO4 but it was not significantly different from that of nebulised albuterol.[249] Nannini LJ[250] found that nebulized MgSO4 had a significant bronchodilator effect in acute asthma and it together with nebulized albuterol, increased the peak flow response in comparison with albuterol plus normal saline. They had used in this study. a single dose of 0.5 mL albuterol (2.5 mg) diluted in 3 mL normal saline or in 3 mL isotonic $MgSO_4$ (225 mg).

In a systematic review by Blitz et al., it was concluded that use of $MgSO_4$ particularly in addition to albuterol produced beneficial effects with respect to increase in pulmonary function and reduced hospital admission.[257] In contrast, the review by Villeneuve et al failed to clarify the role of nebulized $MgSO_4$ and the systemic review by Mohammed S et al. inferred that nebulized $MgSO_4$ had weak evidence of effect on respiratory function and hospital admission in adults.[258-259] Another systematic review by Powell et al showed that when used in addition to beta-2 agonist there is no clear evidence of

improvement with nebulized $MgSO_4$, but they suggest possible improvement in those patients with severe exacerbations of asthma.[260] In a recent systematic review by Knightly et al it was concluded that there was modest benefit in lung function and hospital admission when $MgSO_4$ was added to beta-2 agonist and ipratropium with low confidence in evidence and individual studies suggested that those with severe attacks and attacks of shorter duration experience greater benefit.[261]

Bessmertny et al[254] in a study on adults with mild-to-moderate asthma attacks used nebulized $MgSO_4$ along with albuterol did not find any benefit as against albuterol alone in isotonic saline. During this study, three doses of nebulized albuterol were given at 20-minute intervals followed immediately by nebulized $MgSO_4$ (384 mg) in one group and isotonic saline in the other. Whereas Sarhan et. al[253] in another study using nebulized $MgSO_4$ alone or with albuterol in patients with acute asthma found a significant clinical improvement, increase in PEFR, reduction in heart rate, and reduction in respiratory rate. The response to nebulized $MgSO_4$ alone (100 mg, 3.3% solution) was comparable to that of nebulized albuterol (2.5 mg, 0.5% solution), but it was significantly less than that of nebulized combination of MgSO4 with albuterol both given at 20 minutes interval in 4 doses.

The adverse effects commonly found associated with administration of $MgSO_4$ include nausea, vomiting, flushing, increased thirst, drowsiness, muscle weakness, hypotension, confusion, respiratory depression, cardiac arrhythmias, and loss of deep tendon reflexes.[249] The most common adverse reactions associated with $MgSO_4$ in the study conducted by Sarhan et. al. was dry and a bitter mouth, and dizziness. They did not come across any such adverse effects that will necessitate withdrawal from the study.[253]

Preparation of isotonic, sterile, aqueous solution (3.3% and 4.0%) of magnesium sulphate for inhalation was done in following manner[253]:

a.3 mL dose (3.3% solution, 100 mg)

Magnesium sulphate-$MgSO_4 \cdot 7H_2O$ (246.48 g/mol), 4 gram was dissolved in 100 mL sterile water to which 132 mg of sodium chloride was added and the pH of the solution was adjusted to 3.4, and the total volume was made to 120 mL using the same water and mixed thoroughly. Thereafter, the solution was filtered through a 0.22 μm filter unit and finally 3 ml. of this solution was kept in sterile falcon tubes.

b.2.5 mL dose (4% solution, 100 mg)

Magnesium sulphate-$MgSO_4 \cdot 7H_2O$ (246.48 g/mol), 4 gram was dissolved in 80 mL sterile water. Thereafter the steps were similar as those in the above preparation (a) adjusting a pH of 3.4 and volume of 100 mL. The solution thus prepared was kept in sterile falcon tubes in the quantities of 2.5 ml.

Evidence statement:

- Magnesium sulphate ($MgSO_4$) through intravenous route has been used in severe acute asthma as an additive to the usual bronchodilator therapy. It has been found to have a significant bronchodilator effect.
- Nebulized albuterol in comparison to nebulized magnesium sulphate has a better bronchodilator effect.
- The results with nebulized $MgSO_4$ as an additive to albuterol, when compared with albuterol alone in acute severe asthma, have been found to be variable, with some studies showing enhanced bronchodilator response while others showed no additional benefit of combination.
- Modest benefit in lung function and hospital admission has been seen when $MgSO_4$ was added to beta-2 agonist and ipratropium.
- Nebulized $MgSO_4$ is given as 3 to 4 doses of 100mg each, given every 20 min in addition to other drugs
- The adverse effects commonly associated with MgSO4 nebulization include nausea, vomiting, thirst, flushing, drowsiness, confusion, muscle weakness, respiratory depression, loss of deep tendon reflexes, hypotension, and cardiac arrhythmias. These effects usually do not necessitate withdrawal of therapy.
- Bronchodilator effect as supplement to albuterol, shows modest benefit in lung function, and has impact on hospital admission. Its use was found to be safe

Recommendations:

- We recommend the use of nebulization with magnesium sulphate in 3 to 4 doses of 100 mg each in 3mL (3.3%), given every 20 minutes, as an add on to standard treatment in some refractory cases of acute severe asthma exacerbation. (I A)
- Nebulized magnesium sulphate in cases of severe asthma is recommended only to be used in combination with albuterol, or ipratropium and albuterol both, but not magnesium sulphate alone (I A)
- Nebulized magnesium sulphate is safe to be used in cases of severe asthma (I A)

Q11. What special precautions are to be taken in elderly patients?

The world's population is aging in every country, and they are experiencing growth in the number and proportion of older persons in their population. This growing elderly population is likely to be accompanied by an increasing number of aging patients with asthma and COPD. A good proportion of these patients are likely to be the candidates for the use of nebulizers for their regular medication. Nebulizers in the elderly are largely used to administer inhaled bronchodilators and/or ICS to patients with bronchial asthma and COPD. However, there is relative paucity of evidence to show that nebulizers are better than MDI, particularly when the latter is used in high dose with spacers. A relatively high proportion of elderly patients may not be able to use MDI satisfactorily due to their impaired cognitive function or memory loss, weak fingers, or poor coordination.[18,80,262-263]

The physical and cognitive changes that are common in the elderly, particularly those aged ≥75 years, may interfere with the proper administration of inhaled therapies, leading to insufficient dosing, affecting the treatment outcomes, reducing quality of life, and adding to the economic burden of COPD.[264] Moreover, age-related pulmonary changes may also negatively influence the delivery of inhaled medications to the small airways. In general, these changes include a progressive reduction in compliance of the chest wall, reduction in strength of the respiratory muscles, and anatomical changes to the lung parenchyma and peripheral airways. Changes in thorax shape due to osteoporosis and kyphosis may further add to these problems.[265,266] Further, worsening hypoxia or hypercapnia from COPD or its exacerbation can also negatively impact cognitive function, especially in patients who already demonstrate mild cognitive dysfunction.[267] Loss of physical strength may also contribute to difficulty in actuating a pressurized MDI. The presence of arthritis or joint pain, commonly seen amongst the elderly, may also contribute to an inability to correctly use a handheld inhaler. Neuromuscular conditions like Parkinson's disease or complications after stroke may also interfere with use of these handheld devices.

An early study of cognitively impaired patients who were instructed on inhaler use showed that one day after training, 50% of patients with borderline cognitive impairment and 100% of patients with mild dementia could not operate an MDI correctly.[268] These unaddressed challenges to inhaler selection contribute to inappropriate use of inhalers in 41% - 69% of patients with obstructive airway disease, with critical errors in at least 88% of patients.[269,270]

Often a belief is shared by many of the patients, and some physicians, that nebulized therapy confers benefits over and above those achieved by MDI. Hence, nebulizers, often are used indiscriminately amongst the elderly, but it needs to be verified whether it really scores over MDI, with or without a spacer, using the same drugs and dosages[271] This assumption that nebulizers are superior drug delivery systems than the other handheld devices has been dispelled out by several studies. Mestitz et al, in a four-week randomized, double-blind, placebo-control, crossover trial comparing the acute and chronic effects of terbutaline administered by MDI and nebulizer on 18 patients with stable, severe chronic airflow obstruction, concluded that there is no justification for the preferred outpatient use of nebulized bronchodilators who can use adequate doses of bronchodilators via a MDI.[272] A systematic review including 12 studies with 507 adult patients having acute airways obstruction caused by asthma or COPD, treated in an ED or a hospital, found out that bronchodilator delivery by means of an MDI with a spacer or nebulizer was equivalent in their treatment.[273] There are other published studies also which have demonstrated no clear advantage of nebulizers over MDI's.[274,275]

Overall, there is limited published data on nebulization in elderly patients as most trials exclude old age patients. This necessitates a practical approach, on an individual patient basis, in deciding who should be a proper candidate for the use of nebulizer. Often these clinical decisions tend to be based on results from studies in younger patients. It must be decided beforehand that those amongst these elderlies are unable to use MDI or are not benefited by its use on delivering high dose inhaled bronchodilators as seen by the pulmonary function parameters. Nebulizer treatment for the elderly should also be considered for those patients who are symptomatic despite treatment with conventional MDI or DPI which they are using ineffectively but to the best of their ability.

However, even drug delivery by nebulizers has its own problems. A large percentage of patients, using nebulizers instead of other devices, do so because of physical or cognitive disabilities, but even these disabilities could be a hindrance in the correct usage of the nebulizer, to the extent that even it may necessitate assistance of a caregiver. The problems in these patients with COPD are experienced while using nebulizers at home, at all steps of its use, including problems even prior to nebulization: setting up equipment, fitting of mask, poor understanding of instructions, and time required. Moreover, there also are problems related to the cleaning and disinfection of the nebulizer equipment. The caregiver may be helpful to prepare, administer, and maintain the device. However, despite these problems, a recent survey of 82 patients who were using nebulizers, found that 98% reported that the benefits of nebulizer use outweighed the disadvantages.[276] Therefore, the decision regarding which device should be used to treat the elderly COPD patient should be individualized according to the patient's capabilities and preference.

If unaddressed, these challenges to inhaler selection contribute to inappropriate use of inhalers in 41 to 69% of patients and are accompanied by at least 51% non-adherence to treatment.[277] The available evidence indicates that elderly patients with asthma or COPD find nebulized bronchodilators to be more effective than therapy delivered via a pressurized MDI.[278] In a small survey of patients receiving outpatient nebulizer therapy for chronic lung disease, a majority reported that nebulizer use afforded improved symptom control, well-being, and self-confidence.[60,279]

There are a few things to look out for and take caution while using a nebulizer, such as releases of a mist in the atmosphere, which often may be harmful to the eyes. However, a good fitting face mask helps prevent this problem. A mouthpiece is also sometimes preferred to prevent skin or eye irritation from the circulating mist. Some patients have a preference for a mouthpiece due to its relative ease of use and the ability to synchronise their breathing with aerosol output compared to the facemask.

The management of OAD with nebulization in elderly patients need to take in account, both goals, of symptoms control and reduced risk of side effects, since co-morbidities like ischaemic heart disease, diabetes, osteoporosis, cataract, prostatism, and glaucoma are more common in this age group.[271,280] With advancing age, the side effects of beta2 agonist like cardiotoxicity, skin bruising, osteoporosis and cataract are more commonly seen in these elderly patients.[80,281] Further, the response to bronchodilators also declines with the age, more rapidly to beta2 agonists than to anticholinergics.[282,283] The β-adrenergic response to β_2-agonists decreases with increasing age because of downregulation of these receptors, which explains the higher concentration of drug needed with increasing age to reach the desired clinical effect.[284,285] Hence, the requirement of beta-agonists may go up besides the fact that patients with severe exacerbations may require higher doses.

There are also increasing evidence that the bronchodilator response to anticholinergic agents is less age dependent than the response to beta2 agonists and, on this evidence, it is always recommended that a combination of a beta agonist and ipratropium bromide be given in the elderly patients.[271] In a study by Ullah et al on 29 asthmatic patients they found that response to albuterol declined significantly with age, whereas that to ipratropium did not.[282] In general, for patients aged less than 40 years, albuterol is the drug of choice, thereafter, use of ipratropium needs to be considered. With advancing age, and the apparent decline of beta-adrenergic responsiveness, the initially comparatively small response to ipratropium becomes relatively more important and may even predominate. Hence, in older patients ipratropium may either replace salbutamol, or a combined therapy with both drugs, may be preferable. BTS guideline on nebulization also recommended cautious use of high dose beta-agonist and use of mouthpiece in the elderly patients.[271,280] Long acting selective β_2-agonists, formoterol and arformoterol, may also be useful in the elderly and are considered safe also. Current studies do not support the view that LABA use in older adults is less effective than in younger ages.[286]

Hypokalaemia is another recognised complication of nebulized beta2 agonist therapy and hence baseline potassium levels should be measured, particularly, if patients are on a diuretic or have a poor dietary intake. Hypokalaemia can also occur because of skeletal muscle stimulation by LABA, through vaso-dilation which facilitates intracellular accumulation of potassium, thereby lowering plasma levels. Some studies have shown a dose related reduction in serum potassium level with increasing doses of beta-agonist. This hypokalaemia induced by beta-2 agonists may precipitate arrhythmias in some patients.[65,66] Hence, beta-agonists in the elderly are to be used more judiciously and with more caution with a watch on cardiac and blood parameters.

Evidence statement:

- The aging world's population is likely to be accompanied by an increasing number of older patients with asthma and COPD, many of whom may be the candidates for the use of nebulizers.
- Proper selection of aerosol delivery device between a nebulizer and MDI with spacer, among the elderly, needs to be done considering various factors related to the device and the patient
- Problems related to the use of nebulizer or MDI in this group of patients could be more, leading to their inappropriate use, which need to be identified and addressed to obtain the optimal benefit out of the medication used.
- Nebulization with mouthpiece as the interface is preferable over face masks in elderly to avoid exposure of the aerosol of nebulized drug on the eyes, preventing its adverse effects.
- The advancing age often is accompanied by a decline in response to beta-2 agonists, but not so much to ipratropium, hence, preference be given to combination of SABA with SAMA instead of increasing the dose of beta-2 agonists. Alternatively, SABA may be replaced by SAMA, keeping in view the toxicity to the SABA, especially in presence of co-morbidities in this group of patients. Formoterol and arformoterol use could be another safe option
- Eldery patients more often have comorbidities particularly ischaemic heart disease, glaucoma, prostatism etc. hence high dose beta 2 agonists need to be avoided.

Recommendations:

- Among the elderly in OAD patients, it is recommended to make an appropriate selection between nebulizer and MDI (with spacer), on merits considering various factors related to the device and the patient, to optimize treatment outcomes (UPP)
- Mouthpiece as an interface during nebulization amongst the elderly is recommended as the first choice over the face mask to avoid exposure of drug to the eyes to prevent ocular side effects. (II A)
- For the declining beta-2 agonists response in the elderly, combining use of SAMA to SABA or replacing SABA by SAMA is recommended instead of increasing the dose of SABA, keeping in view its toxicity, especially in presence of co-morbidities in this group of patients. (II A)
- Formoterol and arformoterol use in these patients is also recommended as another safe option (III A)

- Close monitoring for the adverse drug reactions in the elderly, while using nebulized bronchodilators, is recommended, in view of high prevalence of the pre-existing co-morbid conditions in these patients (II A)

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Section - III (Group - C): Nebulization therapy in intensive care unit

Abbreviations

AECOPD - Acute exacerbation of chronic obstructive pulmonary disease
ARDS - Acute Respiratory distress syndrome
BiPAP/BPAP - Bi-level positive airway pressure
BPM - Breaths per minute
cm - Centimetre
CO2 (CO_2) - Carbon dioxide
COPD - Chronic obstructive pulmonary disease
ED - Emergency department
ETT - Endotracheal tube
FEV_1 (FEV1) - Forced expiratory volume in one second
FVC - Forced vital capacity
g - Gram(s)
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
h - Hour
He-O_2 - Helium-Oxygen mixture (Heliox)
HME - Heat-and-moisture exchanger
H_2O - Water
ICS - Inhaled corticosteroids
ICU - Intensive care unit
ID - Identification
I: E - Inspiratory: Expiratory Ratio
L/min - Litres per minute
LABA - Long-acting inhaled β_2-agonists
LAMA - Long-acting muscarinic antagonists
MDI - Metered dose inhaler
mg - Milligram(s)
mg/mL - Milligram(s) per millilitre
mL (ml) - Millilitre(s)
MV - Mechanical ventilation
µ (µm) - Micron (Micrometre)
NIV - Non-invasive ventilation
OAD - Obstructive airway diseases
O_2 - Oxygen
PEEP - Positive end-expiratory pressure
PEEPi - Intrinsic Positive end-expiratory pressure
pMDI - Pressurized metered dose inhaler
RCT - Randomized controlled trial
RR - Respiratory rate
SD - Standard deviation
^{99m}Tc - Technetium -99 micro-aggregates (radiolabelled)
USN - Ultrasonic nebulizer
UPP - Universal practice point
VAP - Ventilator-associated pneumonia
VILI - Ventilator-induced lung injury
VMN - Vibrating mesh nebulizer
Vt (V_T) - Tidal Volume

Introduction

Aerosol therapy, with some or the other form of drugs, is routinely administered in intensive care units (ICU) across the world, in both, patients managed with or without mechanical ventilation as well as those receiving non-invasive ventilation (NIV). The proportion of patients receiving aerosol therapy would differ depending on the type of ICU viz. medical versus

surgical or mixed. In a cross-sectional study, conducted over two weeks, involving 81 ICU in 22 countries, nearly 20% of the patients on mechanical ventilation received aerosol therapy.[1] Another international survey on aerosol therapy that involved 1192 respondents from 611 departments in 70 countries, reported that 99% of them used aerosol therapy during mechanical ventilation and that 95% of the intensivists were using this therapy in their practice.[2]

The delivery efficiency of aerosol devices has significantly improved over the years due to greater understanding of the scientific basis of aerosol therapy in critically ill patients, increased knowledge about optimum techniques for aerosolized medication delivery, and development of newer and more efficient aerosol devices and drugs. There are now a variety of devices available for aerosol therapy in patients on mechanical ventilation and the drug delivery may significantly differ from one device to another. Jet-nebulizers were the most frequently used device (56 %), in one of the studies, followed by metered dose inhalers (23 %).[1] According to another study, various types of nebulizers used for aerosol therapy included jet nebulizers (55%), ultrasonic nebulizers (44%), and vibrating mesh nebulizers (14%). Also, 87% of them thought that ultrasonic nebulizers had better efficacy as compared to jet nebulizers and 69% had no opinion on the use of vibrating mesh nebulizers (VMN)[2] It has also been reported that 50 % of the patients managed with NIV, also received aerosol therapy, predominantly in between the NIV sessions (75%).[1]

There are a number of drugs that are delivered as aerosols in the ICU and the list is gradually expanding. One study showed that bronchodilators, inhaled steroids, and sometimes other drugs including antibiotics were commonly used for aerosol therapy either through nebulizers or through handheld inhalational devices.[1] Another study also reported bronchodilators and steroids as the most frequently used drugs followed by inhaled antibiotics.[2]

Drug efficacy during aerosol therapy depends on the dose delivered through the aerosol and the site of deposition which can be affected by ventilator settings as well as accessories connected to the ventilator. However, the practice of changing ventilatory settings before starting aerosol therapy is not uniform. One multicentre study found that the vast majority of ICU physicians (77%) did not alter ventilatory settings, and only 22% turned off heated humidifiers during nebulization.[2]

Nebulization in mechanically ventilated patients differs from that in spontaneously breathing patients and its use is quite complex. The major difference is that the administration of aerosols is usually dependent on the patient when they are spontaneously breathing while in mechanically ventilated patients it depends upon ventilator circuits, settings, device used as well as the knowledge and experience of healthcare workers administering it. Further, the beneficial effects of inhaled drugs are lesser in patients on MV than in those breathing spontaneously. This might be due to a substantial drug loss caused by the turbulent flow produced by the respiratory prosthesis.[3,4] Various factors that influence aerosol drug delivery to the lung in mechanically ventilated patients include selection of the device and its installation position in the nebulizer circuit, the humidification condition, temperature, gas density, patient position, endotracheal tube size, presence of airway obstruction, adjustment of the ventilator mode and parameters, drug formulation, its dose and frequency applied.[5,6,7] Therefore, physicians and health-care professionals working in ICU need to be aware and adequately trained in proper use of aerosol devices and inhalation techniques for optimum benefit to the patient.

In view of the fact that aerosolized medications are now routinely used for the treatment of critically ill patients, a complete understanding of nebulizer-ventilator interaction is essential for optimization of nebulization therapy in patients on mechanical ventilation. Currently, there are no readily available guidelines which can be followed by ICU physicians and health care providers for delivery of aerosol therapy. This section describes various strategies for effective delivery of nebulized medications in mechanically ventilated patients.

Q1. What are the indications for aerosol therapy in patients on mechanical ventilation (MV) ?

Critically ill patients on MV have frequently been receiving drugs as aerosol for many years to address their special needs.[2,3,8-11] Generally, these therapies are supportive in nature rather than curative and lack high-level evidence supporting their routine use.[12] Physicians in ICU commonly use aerosolized medications for the relief of bronchospasm in patients on MV. One multi-centre study which was conducted in ICU's in several countries reported that the most common indication of aerosol therapy was to relieve bronchoconstriction and airway inflammation.[1]

There are various other reasons for administration of aerosol therapy. All these indications of the aerosol therapy among patients requiring mechanical ventilation may be classified as below:

- *Broncho-dilation:* To relieve the bronchospasm, for example - exacerbation of COPD, asthma, or bronchospasm due to any other cause.
- *Anti-inflammatory:* To control the airway inflammation, for example asthma, COPD, interstitial lung diseases and infections.
- *Mucolytic:* To liquefy tenacious and impacted secretions and help them to be expectorated or suctioned out helping clear the airways
- *Anti-microbial:* To treat pneumonia and other lower respiratory tract infections, for example – tracheobronchitis, cystic fibrosis, ventilator associated pneumonia (bacterial, viral or fungal)
- *Vasoactive:* For treatment of pulmonary arterial hypertension
- Miscellaneous: Heliox for treatment of severe asthma, surfactants in ARDS, broncho-pulmonary dysplasia, humidification of airways

Evidence statement:

- Several drugs and substances have been used for nebulization in patients on mechanical ventilation.
- Common indications for nebulization in these cases include broncho-dilation, anti-inflammatory, anti-microbial, and mucolytic actions.
- Uncommon uses in these patients could be for use of vasoactive drugs, heliox, surfactants, humidification etc.

Recommendations:

- We recommend nebulization therapy commonly for broncho-dilation, anti-inflammatory, anti-microbial, and mucolytic purposes in mechanically ventilated patients (II A)
- Nebulization therapy is also recommended for some other purposes such as use of vasoactive drugs, heliox, surfactants etc in these patients. (IIA)

Q2. What drugs are commonly administered through nebulization in intensive care unit patients?

Delivery of drugs to the lungs using nebulized form has attracted attention of clinicians and researchers for a long time and these have been used for treatment of pathologies localized to lungs as well as for systemic disorders.[13] There are multiple drugs in aerosolized form which have been used for management of critically ill patients in ICU and these include bronchodilators, corticosteroids, antimicrobials, anticoagulants, diuretics, mucolytics etc.[11,14-30] One study from China showed that the most frequently used drugs for aerosol therapy during mechanical ventilation were bronchodilators (64.8%) followed by mucolytic agents (44.2%), inhaled corticosteroids (43.4%) and antibiotics (16.5%).[31] Other authors have also reported bronchodilators, anti-inflammatory (corticosteroids), and antibiotics as the commonly used drugs.[1,2]

Bronchodilators are among the most used drugs in the ICU.[1,2,32] In ventilator-supported patients with airflow obstruction, inhaled bronchodilators are frequently employed to reduce airway resistance and intrinsic PEEP (PEEPi). Aerosolized bronchodilators have also been claimed to enhance muco-ciliary clearance, thus facilitating weaning. However, it is unclear whether regular administration of bronchodilators to a diverse group of patients, other than asthma or COPD, confers any benefit in terms of reduction in the duration of mechanical ventilation, length of ICU stay, length of hospital stay, and in-hospital or long-term mortality.[33] Moreover, aerosolized bronchodilators (β-agonists) have the potential to cause hypokalemia and cardiac arrhythmias.[34,35,36] Further, the use of bronchodilators to a wide spectrum of ventilator-supported patients contributes to additional cost of treatment. However, till date, there has been no attempt to assess the effect of aerosolized bronchodilator therapy on clinically relevant outcomes (ventilator free days, length of ICU or hospital stay, and in-hospital or long-term mortality) among patients on MV in randomized control study.[37,38,39]

There is growing usage of inhaled antibiotics, especially aminoglycosides and colistin for treatment of ventilator-associated pneumonia (VAP) with gram negative organisms. However, at present, the recommendation is to employ inhaled antibiotics as adjunctive therapy for treatment of ventilator-associated tracheobronchitis or VAP due to gram-negative organisms that are resistant to multiple drugs[40,41] A recently published systematic review summarized the studies that assessed in vivo lung delivery of inhaled drugs to mechanically ventilated patients and also there are several drugs that have been used in such animal models. Thus, besides the currently available drugs for nebulization in the management of critically ill patients, several new additions are likely to occur in the future.[11] An updated summary of drugs of interest for nebulization has been provided in Table 1:

Table 1 – Various drugs in use or prospective drugs for use in mechanically ventilated patients[a].

Class of drugs	Name of the drugs
Antimicrobials	Amikacin, Ampicillin, Aztreonam, Cefazolin, Colistin, Gentamicin, Imipenem and cilastatin, Netilmicin, Vancomycin, Tobramycin, Fosfomycin, Levofloxacin, Ciprofloxacin, Amphotericin B, Pentamidine, Ribavirin, Zanamivir, Laninamivir
Anticoagulants	Heparin
Bronchodilator	Albuterol (salbutamol), Levalbuterol (Levosalbutamol), Terbutaline, Atropine, Epinephrine, Fenoterol, Formoterol, Arformoterol, Ipratropium, Glycopyrronium, Magnesium sulfate,
Corticosteroids	Beclomethasone, Budesonide, Fluticasone, Flunisolide, Dexamethasone, Hydrocortisone
Diuretics	Frusemide
Mucolytics	N-acetylcysteine, Ambroxol, Bromhexine, Dornase Alfa, Gomenol, Mesna, Tyloxapol, Mannitol.
Ionic solutions	Hypertonic sodium chloride, Isotonic sodium chloride, Sodium bicarbonate
Anti-diabetic	Insulin
Prostanoids	Epoprostenol, Iloprost, Treprostinil
Surfactant	Synthetic, Bovine-derived, Porcine-derived
Miscellaneous	Perfluorocarbons, Biologicals, Interferon beta-1a, PDE-3 inhibitors, Mycobacterium vaccae, Lignocaine, Tranexamic acid, Opioids, Genes, Heliox

*Based on reference no.11 (Section III) and information from Section IV.

Evidence statement:

- Commonly the drugs used for nebulization in the intensive care unit (ICU) can be for both, treatment of pathologies localized to the lungs as well as for systemic disorders.
- Several drugs have been used in nebulized form in the intensive care unit in mechanically ventilated patients or in animal models as summarized in Table 1.
- Bronchodilators are the most used drugs in the ICU to reduce the airway resistance and intrinsic PEEP.
- The role of bronchodilators in ICU in patients without OAD is uncertain as their usefulness has not been studied through RCTs. Moreover, these drugs have the potential to cause hypokalemia and cardiac arrhythmias; besides adding to the cost of treatment.
- The usage of inhaled antibiotics (mostly aminoglycosides and colistin) in treatment of ventilator-associated pneumonia (VAP), especially with resistant gram-negative organisms is developing mostly as an adjunctive therapy.

Recommendations:

- We recommend use of only those drugs from Table 1 for nebulization which are available commercially and are indicated in patients in an intensive care unit. (II A)
- Nebulized bronchodilators in ventilator-supported patients are recommended only in OAD and not in other diseases for want of RCTs to establish their beneficial effects and also considering issues of their toxicity and cost. (III B)
- Nebulized antibiotics are recommended only as adjunctive therapy in cases of ventilator-associated pneumonia (VAP) with resistant gram-negative organisms.(II A)

Q3. What pre-procedure preparation should be done before administration of nebulization to mechanically ventilated patients?

There could be many barriers to the effective aerosol delivery to ventilator-supported patients, especially the inability of drug particles to negotiate the ventilator circuit and endotracheal tube (ETT). This has also been shown, in some studies, to be responsible for low pulmonary deposition in these patients, compared to ambulatory, non-intubated patients. Thus, the aerosol delivery in mechanically ventilated patients is significantly reduced and this can happen due to several factors[4,9] In a systematic review to assess inhaled drug delivery in mechanically ventilated patients or in animal models; the lung deposition was found to be lower than 20% of nominal dose delivered with nebulizers; and the loss mostly occurred in proximal airways.[11] The passage from the point of generation of the aerosol droplets to the lung must remain clear and this includes the ventilator circuit, the right-angled connector, the in-line suction catheters, the heat-and-moisture exchanger (HME) filter, the artificial airway, and narrowing in the upper airway.

Presence of fluid and secretions in the ventilator circuit, endotracheal tube, as well as in patient's airway, lead to ineffective aerosol delivery due to entrapment of aerosols in the secretions. It is essential to perform a good airway suction prior to nebulization to ensure adequate delivery of aerosol. Presently, there is not enough evidence to support the use of inhaled mucolytic agents in the management of mechanically ventilated patients; further studies are needed. Moreover, there are reports of increase in inspiratory airway resistance after aerosolized administration of mucolytic agents and hence routine use of these agents should be avoided. However, the mucus plugs blocking the artificial airway should be effectively suctioned before administering aerosols.[33,42]

Significant aerosol loss may occur at the connection between the Y-piece and endotracheal tube.[43] Drug particles in the aerosol have difficulty in negotiating the right-angled bend of the connectors. Elimination of sudden changes in the diameter of the ventilator circuit components and a smooth curvature to changes in the path of the aerosols may improve efficiency of aerosol delivery. A streamlining approach that eliminates sudden changes in the diameter of the ventilator circuit components and applies a smooth curvature to changes in the path of the aerosols is a proposed alternative that could lead to improved efficiency of aerosol delivery.[44] The narrowing and roughening of the inner surface of the artificial airway produced by biofilms that may form on its inner surface also acts as an additive effect on aerosol losses, which needs to be taken care of. Similarly, in-line suction catheters can also impede aerosol delivery. Manthous and colleagues demonstrated a significantly higher reduction in airway resistance after using nebulized albuterol on airway resistance in 3 mechanically ventilated patients when they connected the Y-piece directly to the endotracheal tube as compared to the effect observed with an in-line suction catheter and connector in place.[45]

Evidence statement:

- A good airway suction prior to nebulization is essential to ensure adequate ventilation and delivery of aerosol in mechanically ventilated patients since drug delivery is significantly reduced in presence of fluid and secretions in the ventilator circuit, endotracheal tube, as well as in patient's airways.

- Right angled elbow connectors; sudden changes in the diameter, narrowing and roughening of the inner surface of ventilator circuit components; connection between Y piece and endotracheal tube; and in-line suction catheters; reduce the nebulized drug delivery to the lungs.
- Routine use of mucolytic agents may increase the inspiratory airway resistance through their muco kinetic action.

Recommendations:

- Ventilatory circuits are recommended to avoid sharp angles, narrow and sudden changes in the diameter, and need to be characterized by smooth curvatures and smooth inner surfaces. Use of in-line suction catheters should be avoided. (III A)
- Y-piece should be directly connected to the proximal tip of the endotracheal or tracheostomy tube. (UPP)
- It is recommended to have an effective suction of the ventilator circuit, endotracheal tube, as well as in patient's airways before nebulization to remove the fluids and secretions to have better ventilation and drug delivery. (III A)
- Mucolytic agents are not recommended for routine use to avoid inspiratory airway resistance due to increased secretions. (III A)

Q4. Should a heated humidifier be switched off/Heat and Moisture Exchanger (HME) removed during aerosol therapy on MV?

The heat and humidity of an inhaled gas to body temperature and pressure saturated conditions promotes normal muco-ciliary clearance, prevents drying of the airway mucosa, and reduces bronchospastic responses, compared to breathing cold dry air. Some degree of circuit humidification is always used during mechanical ventilation. Humidification in the ventilator circuit decreases aerosol deposition by approximately 40% compared to dry circuits at room temperature, probably due to an increase in aerosol particle size, leading to increased particle loss in the circuit. The impaction losses are increased with the larger size particles.[46,47,48] Turning off the heated humidifiers during brief periods of nebulization (10-15 minutes) may not be a problem as the effects of dry gas on the airway mucosa are minimized but if nebulization is used for longer periods humidifiers off may lead to mucosal injury. (48.) A higher dose of the drug may be used if the humidifier is not switched off during nebulization especially with the inexpensive drugs, such as salbutamol or ipratropium bromide, where increasing the dose may be safer than turning off the humidifier.[45,49] Humidifiers should always be switched off for drugs which are costly and heat unstable such as antibiotics, as this will be more cost-effective.

In a survey among units using heated humidifiers, only 22 % of respondents (n = 136) reported stopping heated humidification systems during nebulization.[2] However, by switching off an active heated humidifier, during nebulization, the decrease in humidity and temperature is usually gradual, taking up to 20 minutes, making the benefit on nebulization questionable. Also, the patient exhaling humid air and the presence of condensation in the circuit keeps absolute humidity high.[49] Some authors recommend that there is no need to switch off the humidifier while delivering aerosol to the ventilated patients, unnecessarily exposing them to the risk of receiving dry gas, which might harm the lungs.[50]

Heat and moisture exchangers (HME) capture the heat and moisture from the exhaled breath and transfer part of the heat and humidity to the next inspired breath making it humid. They are commonly employed to provide humidification of inspired air during mechanical ventilation. The HME filter can also capture drug particles in the aerosol, further reducing the efficiency of drug delivery markedly. Therefore, whenever an HME is used, it should be removed from the circuit as it markedly reduces the aerosol delivery. Some manufacturers recently have introduced HMEs that accommodate aerosol delivery. In these HMEs, the inspiratory gas flow bypasses the filter in the HME during aerosol delivery so that adequate aerosol delivery is possible without removing the HME from the circuit.[51]

Evidence statement:

- Some degree of humidification is always used during mechanical ventilation for the normal functioning of airway mucosa. Heated humidifiers have been shown to increase the droplet size and reduce drug deposition during nebulization.
- Heated humidifiers need to be turned off during the brief periods of nebulization (10-15 min), avoiding longer periods, however, usefulness of this practice is questionable as it takes up to 20 min. for heat and humidity to settle.
- Higher doses of the drug may be used if the heated humidifier is not switched off during nebulization to compensate for the loss, but these must be switched off for drugs which are costly and heat unstable (e.g. antibiotics).
- Heat and moisture exchanger (HME) hampers drug delivery, hence it must be removed during nebulization, except for the newer models with provision to bypass the filter in the HME during inspiratory gas flow.

Recommendations:

- Heated humidifiers are recommended to be switched off during nebulization for brief periods (10-15 min.), but longer periods need to be avoided. However, its usefulness has been disputed. (III A)
- It is recommended to use higher doses of drugs to compensate for the loss if heated humidifiers are not switched off, but for expensive and heat unstable drugs, it must be switched off to prevent drug loss. (III A)

- Heat and moisture exchanger (HME), which can hamper drug delivery, should be removed from the circuit during nebulization, except in newer models with provision to bypass the filter in HME during inspiratory flow. (III A).

Q5. What type of nebulizer should be used for patients on mechanical ventilation?

Pressurized metered-dose inhalers (pMDIs) are commonly used for administering inhaled drugs to mechanically ventilated patients because they are cost-effective, convenient, reliable, and safe. However, the efficiency of drug delivery with pMDIs is very dependent on the configuration of the device and technique of administration which leads to a lot of variations in the drug delivery.[52] Therapy with pMDIs can be ineffective if careful attention is not given to the appropriate technique of administration.[34] Connecting the pMDI to a spacer chamber increases aerosol deposition in the airways with improved potential for clinical response. However, it is to be seen that the prescribed drugs are available in this dosage form since the options are limited.[27,53]

Besides pMDI, the other option for aerosol therapy during mechanical ventilation is to use a nebulizer. It has been shown that nebulizers and MDIs have similar effects on lung function, both types of devices resulting in equivalent changes in FEV1. Three types of nebulizers are available for this purpose, and these include Jet, ultrasonic and vibrating mesh nebulizers.

The efficiency of jet nebulizers for aerosol production is highly variable even among different batches of the same brand of the device.[54,55] A separate nebulizer unit powered by pressurized gas from a compressor is usually required for continuous aerosol generation. The addition of this additional flow into the ventilator circuit, through a jet nebulizer, is a major disadvantage as it affects delivered volume and flow to the patient. Use of a jet nebulizer during MV entrains an additional 6 −8 L/min of gas into the ventilator circuit, which influences the tidal volume delivered to the patient. The jet nebulizer may also cause circuit contamination and have an inconveniently long treatment time besides requiring equipment set up prior to the procedure and proper cleaning after it.[33]

Jet nebulizers may also inactivate or denature the drug due to shear forces.[54,56] The temperature of the reservoir fluid decreases about 15 degrees C during nebulization which may affect the concentration of the drug and alter other characteristics of the aerosol. The residual volumes of jet nebulizers are greater than those of ultrasonic and mesh nebulizers which is a major factor associated with their lower aerosol delivery efficiency.[57,58,59] Although most jet nebulizers are operated continuously, these may also have the option of having continuous or intermittent functioning. Intermittent nebulizers are said to be more efficient as these generate aerosols only during inspiration and eliminate changes in ventilator parameters during aerosol therapy besides preventing loss of aerosol during expiration. Jet nebulizers are easy to use, and inexpensive compared with mesh and ultrasonic nebulizers but are variable in performance, which is an important issue for the delivery of inhaled medications to critically ill patients. Still, jet nebulizers continue to be commonly employed in ventilator-supported patients because of the operator's familiarity with their use.

Ultrasonic nebulizers (USN) can produce higher aerosol output requiring a shorter time of operation than jet nebulizers.[57] Advantages of the USN include the absence of a driving gas flow being added to the circuit, which can change the ventilator parameters and alarm setting, besides having a potential to deliver a greater volume of medication to the lungs. Ultrasonic nebulizers have not been popular for aerosol delivery during mechanical ventilation due to several problems. These are not efficient in nebulizing suspensions and the aerosol particle size generated is larger with ultrasonic nebulizers, as compared to jet nebulizers.[60,61,62] The nebulizer device is usually of large size though small volume ultrasonic nebulizers with smaller residual volumes are also available. Ultrasonic nebulizers are much more expensive than jet nebulizers, and like them, the drug solution becomes more concentrated during operation as the solution temperature increases by 10-15 degrees C after 10 minutes of nebulization, which has the potential to denature some of the drug formulations. (60,61) Therefore, the cost, the size of the machine, and their inefficiency in nebulizing suspensions and viscous solutions make them undesirable for aerosol therapy in critical care.

The newer generation, vibrating mesh nebulizers (VMN), available now for use during mechanical ventilation, are more efficient than the jet or ultrasonic nebulizers. These are superior to the jet nebulizer in aerosol drug delivery and in its ability to operate without adding gas to the circuit.[34,63,64] The VMNs have a high rate of nebulization and drug output is 2-3 times higher than with jet nebulizers because their residual volume is negligible (ranging from 0.1 mL to 0.5 mL) and thus, the dose of drugs to be administered for clinical response could be reduced compared to jet and USN's.[65-67] The temperature of the solution also does not change during operation of the VMN and thus allows protein compounds (non-bronchodilator drugs) for nebulization. Their operation is also quieter than jet nebulizers.[33]

Unlike jet nebulizers, mesh nebulizers are powered by electricity or battery and are not affected by variations in the gas flow. However, like the jet and ultrasonic nebulizers, these too have some disadvantages, e.g., their pores getting clogged with some suspensions or viscous drugs, besides being much more expensive than jet nebulizers. Even though the pores of VMN could get clogged by suspensions or viscous drugs, this is without making a noticeable difference to the nebulizer output.[68] However, these may be more cost-effective over time and are preferred over the jet nebulizers. The differences in delivery efficiency between mesh and jet nebulizers may be 3-fold; therefore, drug doses may need to be adjusted to eliminate adverse effects that may occur due to overdose.[69,70,71]

Evidence statement:

- The efficiency of jet nebulizers for aerosol production is highly variable in their performance, even among different batches of the same brand, which raises concerns about the delivery of inhaled medications to critically ill patients.
- Jet nebulizers continue to be commonly employed in ventilator-supported patients since these are easy to use, and inexpensive compared with mesh and ultrasonic nebulizers, and because of the operator's familiarity with their use.
- The problem of additional flow of gas (6–8 L/min) from the compressor of the jet nebulizer into the ventilator circuit affecting the delivered volume and flow to the patient; besides having a longer treatment time and risk of circuit contamination; are its additional drawbacks.
- Jet nebulizers may inactivate or denature some of the drugs due to the shear forces and fall in the temperature of the reservoir fluid up to 15 degrees C during nebulization. This also can alter the drug concentration and the characteristics of the aerosol.
- The larger residual volumes after nebulization with the jet nebulizers result in lower aerosol delivery efficiency.
- The jet nebulizers continue to be commonly employed even though VMN has better drug delivery as compared to them.
- Ultrasonic nebulizers have the benefit of producing higher aerosol output, shorter nebulization time, and with no additional driving gas to the circuit affecting the ventilatory parameters. However, their cost, large size, and rise of solution temperature with the potential to denature some of the drug formulations make them undesirable for aerosol therapy in critical care.
- Vibrating mesh nebulizers (VMN) are more efficient than the jet or ultrasonic nebulizers, operate without adding gas to the circuit; with no change in temperature of drug solution; higher drug output with negligible residual volume. This increase in drug delivery requires dose adjustment to eliminate possible adverse effects due to overdosage.
- The VMN nebulizers are more expensive besides the fact that some of the suspensions or viscous drugs may clog the pores of the mesh affecting their performance.

Recommendations:

- Vibrating mesh nebulizers are recommended over the jet and ultrasonic nebulizers in mechanically ventilated patients due to their better efficiency, operation without adding extra gas to the circuit, and causing no change in temperature of the drug solution. Clogging of the pores of their mesh on using suspensions and viscous solutions is a problem faced with them. (III A)
- The additional flow of gas (6–8 L/min) from the compressor of the jet nebulizer into the ventilator circuit affects the delivered volume and flow to the patient which is not desirable. (III A)
- Denaturing the drug in the jet nebulizer, due to its sheer forces and due to lowering of temperature of drug solution by 15-degree C.; longer nebulization time; lower aerosol delivery efficiency and contamination of the circuit, are the other problems faced with it. (III A)
- Jet nebulizers, despite several disadvantages and their variable performance, continue to be used more frequently, due to operator's familiarity and ease of their operation, and for being less expensive. (III A)
- Pressurized metered-dose inhalers (pMDIs) continue to be recommended as an option for the drug aerosol delivery in mechanically ventilated patients as these have been shown to be equally effective to the nebulizers. (III A)

Q6. Where should the nebulizer be attached in the ventilator circuit for maximizing aerosol delivery?

It has been observed that the aerosol delivery is reduced in the artificial airway in a tracheal intubated patient.[33,72] Macintyre and colleagues first reported that, in these intubated patients, aerosol transmission was only one-sixth of non-intubated patients[4] Over the past few decades, with the newer technologies, the aerosol delivery to invasive MV patients has almost been matched and it has even exceeded those with non-artificial airways.[32,52,59] Many factors affect the delivery of aerosols to the lungs which have been related to patients, drugs, devices, artificial airways, ventilator settings, ventilator circuits; and the position of nebulizer in the ventilator circuit itself.[48,73-77] The position of the nebulizer in the ventilator circuit is one of the crucial factors that influences the efficiency of aerosol delivery to a large extent. Its placement with the jet nebulizer between the endotracheal tube and the Y-piece is least useful for aerosol delivery. However, in clinical practice, the commonest nebulizer position was found to be between the tracheal tube and the Y-piece (41~46%) or after Y-piece (39~41%), and in other positions in 10~20% patients.[1,2] Another study also showed that the nebulizer was usually placed between the tracheal tube and Y-piece and after the Y-piece.[31]

Several in vitro experiments have shown that, when the nebulizer was placed in different locations, aerosol delivery changed in both adult and paediatric lung models. Previous studies reported that placing the jet nebulizer farther from the endotracheal tube improves drug delivery, leading to the recommendation to place the nebulizer proximal to the humidifier close to the ventilator. ,[46,69], [78–83] It was believed that placement of a jet nebulizer farther away from the endotracheal tube improves aerosol delivery because the ventilator tubing acts as a spacer in which the aerosol accumulates in-between the breaths. The continuous aerosol generated from the jet nebulizer fills the inspiratory limb between inspirations, thus increasing the proportion of drug output delivered with each breath. Many in vitro tests showed that, when the nebulizer was

placed after Y-piece or between the ventilator inlet and heated humidifier, drug delivery to the lungs was the largest. ,[81 84-86] The efficiency is reduced when the nebulizer was placed at Y-piece or between Y-piece and the tracheal tube. ,[69,80,8185-87] However, there have been fewer in vivo experiments to show how different nebulizer positions affect aerosol delivery.

Ari et. al.(2010) compared the position of nebulizer with Jet and VMN in simulated paediatric and adult lung models using nebulized albuterol sulphate. Two nebulizer positions were used:[1] jet nebulizer 15 cm from the Y-piece adapter, and VMN attached directly to the Y-piece; and[2] jet nebulizer prior to the heated humidifier, and VMN at inlet to the humidifier. Nebulizer placement prior to the humidifier increased drug delivery with both the nebulizers, with a greater increase seen with VMN, showing 2-4-fold greater increase at all positions ($P < .05$) in both lung models. The jet nebulizer was the most efficient in position 15 cm from the ventilator.[69]

In another study Ari et al compared drug delivery from jet, VMN, and ultrasonic nebulizers(USN), in a model of MV, placed at three different positions, again using albuterol. The three positions chosen were 1) between the endotracheal tube and the Y-piece;[2] 15 cm from Y-piece; and[3] 15 cm from the ventilator. They found that the VMN and USN were most efficient when placed 15 cm from Y-piece (position 2) and in contrast, the jet nebulizer was most efficient in position 3.[81] Hughes et al and Quinn also found that lung dose increased when the generating device was placed closer to the ventilator.[83,88]

Moraine et al. in a study over 38 mechanically ventilated patients, delivering ipratropium through ultrasonic nebulizer, found that placement of the nebulizer near the ventilator before the humidifier, did not affect the urinary excretion of the drug, compared to placement at the end of the inspiratory limb before the Y-piece. They concluded that the position of the nebulizer in the ventilatory circuit had no effect on the pulmonary bioavailability of ipratropium.[89]

In another study on a paediatric model by Berlinski and Willis (2013), using different nebulizers, VMN was found to be the most efficient device. All the nebulizers (two Jet, ultrasonic, and VMN) were found to be more efficient when placed at either the ventilator or the humidifier, and less efficient when placed at either the Y-piece or 30 cm from the Y-piece. The VMN outperformed both jet nebulizers at all tested positions, and the USN when placed at either the ventilator or the humidifier.[85,90]

However, the limitation of all these studies was that these were conducted in vitro. In vivo studies are needed to draw definitive conclusions.[87] Another reason may be that different drugs have been studied in different studies which can also affect the results.[90]

In a recent randomized clinical trial, Zhang et.al. (2021) exploring the best nebulizer position for aerosol delivery of salbutamol through jet atomizer, within the MV circuitry, 75 intubated patients with respiratory failure were randomly divided into three groups according to the position of the nebulizer. In group A the position was between the tracheal tube and Y-piece, in group B, it was at the inspiratory limb 80 cm away from the Y-piece and, for group C, between the ventilator inlet and the heated humidifier. The serum and urine salbutamol concentrations were measured which was highest in group B, followed by group C, and the lowest in group A, showing a significant difference between the three groups ($P < 0.05$). The difference was also found statistically significant between groups B and A ($P = 0.001$; $P = 0.002$, respectively) but there were no significant differences observed among the other groups. Thus, the drug concentrations were highest when the nebulizer was placed 80 cm away from the Y-piece, while the location near the patient (Group A), was having the lowest drug concentration. The group B location could permit the pipeline to store mist and increase aerosol delivery.[91] Thus, placement of the jet nebulizer between the Y-piece and the endotracheal tube is least useful for aerosol delivery. The aerosol delivery is increased when the jet nebulizer is placed at a distance of at least 30 cm from the endotracheal tube, and the recent RCT has shown a position at 80 cm. from the Y-piece in the inspiratory limb to be the most suitable.[69,91]

There are also some other contributory factors for improved nebulization. It has been observed that aerosol production is 2-fold more in a dry environment (i.e., before the humidifier) where the aerosol particles are also smaller and more stable.[69] It was also seen that during conventional ventilation with no bias flow, placement of nebulizer proximal to the ventilator reduces drug delivery compared to placement proximal to the patient.[69] Though it seems counterintuitive to place an aerosol generator before the humidifier, it was noted that in the presence of bias flow, the delivery efficiency of the VMN was higher when it was placed in proximity with the ventilator. However, both Berlinski and Willis, and Ari et al. showed that in the presence of bias flow, placement of a VMN at the ventilator improved delivery efficiency in adults and children.[47,48,81,92]

Evidence statement:

- The aerosol delivery is reduced in an artificial airway in patients who are tracheally intubated as compared to patients without artificial airways. However, with the advancing technologies this gap is getting reduced.
- Position of the nebulizer in the ventilator circuit can influence the efficiency of the aerosol delivery. However, some of the studies have also concluded that position had no effect on its efficacy.
- Placing a jet nebulizer between the endotracheal tube and the Y-piece has the least usefulness for the aerosol delivery. However, during clinical practice mostly it is placed in this position.
- Several in vitro studies on the lung models show that jet nebulizers have a better efficacy when placed at 15 cm from ventilator end.
- One of the RCT recently has shown that the optimal position of the nebulizer is 80 cm away from the Y-piece and that the aerosol delivery was lowest between Y-piece and the tracheal tube.

- The ultrasonic nebulizers and/or VMN on the lung models show a better efficacy at 15 cm from Y-piece in inspiratory limb, or at ventilator or humidifier (away from the Y-piece). Efficacy is less at the Y-piece. Variations in positions in between various experimental studies have also been found.
- Delivery of bronchodilators with the VMN is 2-4-fold greater compared with jet nebulizers placed at multiple positions in the artificial airways ($P < 0.05$). With an efficient nebulizer (VMN) the position of the nebulizer may not have much effect.

Recommendations:

- Position of a jet nebulizer at 80 cm away from the Y-piece is the recommended position for its optimal effect during mechanical ventilation (II A)
- Vibrating mesh nebulizer is recommended as the device of choice in these patients and it is to be connected at 10-15 cm from the Y-piece in the inspiratory limb. (III A)
- Much significance is not to be given to the position of nebulizer as it does not significantly affect the pulmonary bioavailability of bronchodilators, especially so with VMN. However, a position between the endotracheal tube and Y-piece is not recommended (UPP)

Q 7. What is the preferred position of a patient for aerosol therapy administration while on MV?

Spontaneously breathing patients usually adopt a sitting or standing posture during aerosol inhalation. In contrast, most patients are recumbent or semi-recumbent while receiving mechanical ventilation and inhaled drug therapy.[33] In ventilator-dependent patients, sitting position has been demonstrated to improve drug delivery by Dhand and Guntur.[72] However, in another study the delivery time was not found to differ significantly between sitting and side lying positions (mean difference 0.58 min.).[93] Small prospective studies have evaluated the efficacy of bronchodilators like salbutamol, salmeterol, and ipratropium in patients on mechanical ventilation. In these studies, aerosol therapy could be effectively administered in a semi-recumbent position with the head end elevated 20 to 30 degrees above horizontal position.27, 63, [94-99] However, none of the studies compared the semi-recumbent position with any other position. Antimicrobial agents have also been delivered using standard practices of bronchodilator therapy administration in prospective studies and randomized trials.[100] International consensus statements do not specify the preferred position of the patient during aerosol therapy on mechanical ventilation.[101]

Evidence statement:

- Semi-recumbent position with head end elevated 20 to 30 degrees, for effective delivery of bronchodilators in patients on mechanical ventilation, has been found to be suitable. Antimicrobial agents can also be delivered in the same position.
- No studies comparing semi-recumbent positions with any other patient positions for aerosol delivery are available.
- International consensus statements also do not specify any specific position of patient.

Recommendations:

- Patients on mechanical ventilation, for the aerosol therapy, are recommended to be kept in semi-recumbent position with head end elevated to 20 to 30 degrees above horizontal position. (II A)

Q 8. What should be the ventilatory settings while administering nebulization?

Ventilatory circuit designs may also have important implications on aerosol delivery in patients on mechanical ventilation besides the ventilatory settings. These include size of the endotracheal tube (ETT), acute angulations in the circuit and inner surface of the circuit. Though small size ETTs have been associated with lower aerosol deposition in paediatric studies, no significant difference has been demonstrated in adult studies comparing ETT sizes of 7 French and 9 French.[102,103]

Aerosol deposition in tracheostomy tubes has not been studied in as much detail as with ETTs. O'Riordan and colleagues[104] found that approximately 10% of the nominal dose from a nebulizer is deposited in the tracheostomy tube of mechanically ventilated subjects. Ari et. al.[105] reported a greater percentage of the dose delivered via a tracheostomy tube compared to an ETT in a bench model of mechanical ventilation using either jet nebulizer or pMDI. Another in vitro study found that removing the inner cannula of the tracheostomy tube prior to aerosol administration in a vitro study increased drug delivery.[106] In another study on mechanically ventilated patients, there was similar aerosol delivery in patients on tracheostomy as compared to ETT ($P < 0.12$) when 99mTc-labeled fenoterol was delivered by pMDI and spacer.[107]

Modification of ventilatory settings is an important aspect to optimize aerosol delivery in patients on mechanical ventilation. Fink et al evaluated the effects of various ventilatory settings including modes of ventilation, flow pattern, humidity, and spontaneous respiratory efforts on salbutamol aerosol delivery in an airway model. In this study, salbutamol delivery was significantly lower ($P<0.01$) during mechanical ventilation as compared to spontaneous breaths. Delivery was significantly greater in dry (28.8 to 39%) than humidified conditions (15.9 to 20.2%) with $p < 0.005$ in all ventilatory modes. Longer duty cycle, i.e., ratio of inspiratory time to total breathing cycle time was associated with a significant increase in aerosol deposition ($p<0.05$). Also, there was a linear correlation of drug deposition with both inspiratory time and duty cycle (coefficient of correlation, $r > 0.91$).[108]

Hess et al[109] reported similar results during mechanical ventilation using jet nebulization. It was also found that aerosol delivery was significantly lower during pressure-controlled ventilation as compared to volume-controlled ventilation ($p = 0.03$). In another study, lower inspiratory flow rate (40 versus 80 L/min; $p < 0.001$), longer duty cycle (0.50 versus 0.25; $p < 0.04$), and a shorter interval between successive MDI actuations (15 versus 60 s; $p < 0.02$) resulted in increased aerosol delivery.[43] Addition of end inspiratory pause of 5 seconds did not affect efficacy of salbutamol in mechanically ventilated patients of COPD in a prospective study.[95]

In a randomized study involving 17 patients with respiratory disease on mechanical ventilation who received aerosols using VMN, volume-controlled ventilation was associated with significantly higher drug deposition as compared to pressure support mode (15.1% vs 10.5%, $p < 0.05$). Pressure support mode resulted in higher deposition of aerosol in the endotracheal tube and trachea as compared to volume control ventilation (27.4% vs. 20.7%, $p < 0.05$).[110] Constant inspiratory flow was associated with better delivery of aerosolized amikacin in one in-vitro study.[111]

The bias flow may also influence the aerosol deposition. Ari et. al. reported that increasing bias flows decreased the amount of aerosol deposition; they recommended lower bias flows (≤2 L/min) for greater aerosol delivery with nebulizers operating continuously. The impact of bias flow is greater for jet nebulizers than for VMN.[69]

Settings associated with optimal deposition of aerosolized antibiotics in mechanically ventilated patients include volume controlled modes, constant low inspiratory flow patterns(30–50 L/min), higher tidal volumes 500ml or more in an adult (Vt 8 ml/kg), longer inspiratory time, and slower inspiratory flows (30–50 L/min) improve aerosol delivery.[43,46,108] Drug delivery is linearly correlated with a longer duty cycle (inspiratory time/total breath duration). Other settings are a higher inspiratory to expiratory time ratio (I:E ratio 1:1), respiratory rate of 12 to 15 breaths per minute, inspiratory pause for 20% of duty cycle, and short acting sedative administration to optimize drug delivery. In patients of COPD, application of an optimal positive end expiratory pressure (PEEP) of 5 to 10 cm H20 enhances the bronchodilator effect of albuterol and thus the net effect is reduction in the level of PEEPi due to the effect of combination of albuterol and external PEEP[33,98] In contrast, Guérin and colleagues reported that after administration of nebulized fenoterol, respiratory mechanics improved when PEEP was set at zero.[112]Vibrating mesh nebulizers have been preferred to jet nebulizers due to better aerosol delivery.[101,113]

Operating a jet nebulizer at a higher gas flow during mechanical ventilation decreases treatment time needed to deliver the specified amount of drug to mechanically ventilated patients, but this may increase 6-8 L/min of gas flow into the ventilator circuit, which influences the tidal volume delivered to the patient. This increase in the tidal volume needs to be adjusted to account for this additional volume, but this correction is not precise.[33]

Evidence statement:

- Small size of the endotracheal tube (ETT) in paediatric studies is associated with lower aerosol deposition but no significant difference has been shown in adult studies comparing sizes of 7 and 9 French.
- Aerosol deposition in patients with tracheostomy tubes has not been well studied and different studies show contradictory findings.
- Drug delivery is significantly greater in dry than humidified conditions inside the mechanical ventilation circuit.
- A longer duty cycle and inspiratory time are associated with significant increase in aerosol deposition.
- Volume-controlled ventilation was associated with significantly higher drug deposition as compared to pressure support mode (Higher deposition in proximal airways)
- The bias flow also has effect over aerosol deposition, increasing bias flow decreases the amount of aerosol deposition and this influence is more with jet nebulizer than VMN.
- Ventilatory settings for the optimal deposition of drug include, volume-controlled mode; higher tidal volumes of 500ml or more in an adult (Vt 8 ml/kg); lower inspiratory flow rate (30–50 L/min), higher inspiratory to expiratory time ratio (I:E ratio 1:1); longer duty cycle and inspiratory time; inspiratory pause for 20% of duty cycle; respiratory rate of 12 to 15 breaths per minute; lower bias flow; optimal positive end expiratory pressure (PEEP) of 5 to 10 cm H20; and short acting sedative administration to avoid asynchrony. These were associated with increased aerosol delivery in mechanically ventilated patients undergoing nebulization.
- Vibrating mesh nebulizers have been preferred to jet nebulizers due to better aerosol delivery.

Recommendations:

- There are no specific recommendations regarding the size of the endotracheal tube (ETT) in adult patients on mechanical ventilation undergoing nebulization and in those having tracheostomy tubes. (III A)
- It is recommended to have dry conditions in the mechanical ventilation circuit to have greater aerosol deposition in the airways. (II A)
- Following ventilatory settings are recommended in a mechanically ventilated patients undergoing nebulization: (II A)
  -Volume-controlled ventilation
  -Higher tidal volumes 500ml or more in an adult (Vt 8 ml/kg)
  -Lower inspiratory flow rate (30–50 L/min)
  -longer inspiratory time, and slower inspiratory flows improve aerosol delivery.

-Higher inspiratory to expiratory time ratio (I:E ratio 1:1)
-Longer duty cycle and inspiratory time
-Inspiratory pause for 20% of duty cycle
-Respiratory rate of 12 to 15 breaths per minute
-Lower bias flow
-Optimal positive end expiratory pressure (PEEP) of 5 to 10 cm H20
-Short acting sedative administration to avoid asynchrony.
-Use of vibrating mesh nebulizer is preferable.

Q. 9. What is the place of Heliox (helium and oxygen mixture) in nebulized drug delivery to the lungs in mechanically ventilated patients?

Helium is an odourless, non-explosive and biologically inert gas which has been used as a 70/30 mixture of helium and oxygen (Heliox) in clinical practice for many decades in the treatment of upper and lower airway obstruction; however, its role in the treatment of patients with severe asthma, exacerbations of COPD, or bronchiolitis has provided mixed results.[114,115] Cambonie et al. reported that heliox was shown to decrease the length of stay in patients with severe respiratory distress in the ICU.[116] In mechanically ventilated patients with severe asthma, inhalation of heliox decreases airway resistance and the alveolar-arterial oxygen gradient and improves carbon dioxide elimination.[117,118]In patients receiving non-invasive ventilation for acute exacerbations of COPD, heliox reduces dyspnoea and work of breathing and improves gas exchange.[119,120]

The density of the inhaled gas influences drug delivery in mechanically ventilated patients. High inspiratory airflows are often employed during mechanical ventilation which can create turbulence in the airflow leading to increased particle impaction and thus more deposition in the proximal airways.[121] Inhalation of less dense gas, such as heliox, makes airflow less turbulent and more laminar, facilitating inhaled drug delivery.[122,123]Albuterol delivery from an MDI was found better with a 70/30 heliox than with a 70/30 nitrogen-oxygen mixture in a paediatric model of mechanical ventilation.[124] Similarly, in a bench model of adult mechanical ventilation, the drug delivery was 50% higher with 80/20 heliox than with oxygen[82] Thus, there was an inverse relationship between the density of the gas mixture and drug delivery. In contrast, nebulizer operation with heliox reduced drug output and respirable mass and drug output from the nebulizer positively correlated with gas density.[82,123] Hence, to maximize pulmonary deposition of nebulized aerosol in a ventilated patient, one must operate the nebulizer with oxygen (at a flow rate of 6–8 L/min) and have ventilator circuit containing heliox.[49] Lin. With this method, aerosol delivery to the lower airways of a tracheobronchial model was 50% higher with helium-oxygen than with oxygen in the ventilator circuit.[82] In order to achieve a high yield of drug output from a nebulizer using heliox, continuous operation of the nebulizer at a high flow rate of 15 L/min, is required to match the efficiency achieved with O2 at 6 L/min. Use of such continuous high flows of heliox through the circuit would waste gas, and require re-adjustment of minute ventilation settings during nebulizer operation which is not desirable.[122]

It is also important to know that heliox may adversely affect the function of some ventilators, and therefore the system must be tested before using it, in order to prevent detrimental effects on patients.[77,125] Moreover, treatment with heliox is costly and technically complex, and its role in the treatment of mechanically ventilated patients has yet not been established.[126]

Evidence statement:

- Heliox, a 70/30 mixture of helium and oxygen, is a low-density gas, which has been used in clinical practice for many decades in the treatment of upper and lower airway obstruction.
- Heliox may improve the aerosol deposition in the lungs during mechanical ventilation, but its use is technically complex, besides being expensive, and its usefulness in these patients has not yet been established.

Recommendations:

- Routine use of heliox in mechanically ventilated patients, though may improve nebulized drug deposition, is not recommended for being more expensive and technically complex to use. (II B)

Q 10. Should aerosol therapy during non-invasive ventilation (NIV) be administered via ventilator circuit while continuing NIV, or independently after discontinuing NIV?

NIV is often used in patients having acute and chronic respiratory failure and a sizable number in this population require aerosolized medications, commonly bronchodilators, delivered sometimes even without interrupting the respiratory support.[127] There is currently no commercially available system designed specifically for aerosol delivery during NIV.[128] In a recent international survey, 99% of physicians used some sort of aerosol therapy during MV including NIV, and nearly 50% of patients undergoing NIV received nebulization. However, the majority of patients (75%) received nebulization in between NIV sessions rather than via NIV circuit.[1,2] In a small prospective study on 19 patients with acute exacerbation of COPD, NIV could be safely discontinued for short duration to administer aerosol therapy. However, even short-term cessation of NIV may not be feasible in all patients.[129]

Combination of NIV along with nebulized aerosol therapy has been shown to be more efficacious than aerosol therapy alone in terms of spirometric variables in patients with asthma.[130] An observational study did not find NIV to alter aerosol delivery efficiency of nebulizer as compared to conventional nebulization with a face mask interface.[130-131] In another study by Gupta et al[131] the combination of aerosol delivery and NIV was found to be a complicated relationship between delivered dose and patient improvement. The results of this *in vivo* study with oro-nasal mask, delivering bronchodilators to 53 asthmatic patients, showed that ICU and hospital stay durations were decreased by the combination of aerosol therapy and NIV as opposed to aerosol delivery alone. No significant differences were observed to occur in the spirometry data, although the mean dose of bronchodilator decreased significantly suggesting that the addition of NIV reduced the needed amount of bronchodilators.[131,132] Among healthy adults in a study, jet nebulizer delivered lung technetium-99m was comparable among spontaneously breathing subjects as compared to those on continuous positive pressure ventilation (10 cm H2O) or BiPAP (10/5 cm H2O).[133]

Salbutamol delivered via NIV circuit resulted in significantly higher peak expiratory flow rate in a prospective convenience-randomized study involving 100 asthmatic patients with acute asthma exacerbation, with similar improvements in oxygen saturation, heart rate and respiratory rate.[134] Similar results were reported in other prospective randomized studies, with comparable drug deposition.[135,136] However, data on aerosol therapy coupled with NIV in this special patient population is scarce, and there is a need for prospective randomized trials to manage these cases more precisely.[137] There is also limited literature on effects of humidification on aerosol delivery during non-invasive ventilation.[127]

In paediatric NIV models, nebulizer positioned at the mask or before the Y-piece of the double-limb circuit provided the highest aerosol delivery. Various studies on aerosol therapy in single limb NIV circuits have demonstrated the best position of the nebulizer to be between the exhalation port and the lung.[138,139] One of the studies also evaluated aerosol delivery of salbutamol using jet nebulizer with various ventilatory settings, i.e., inspiratory and expiratory pressures (10/5, 15/5, 20/5, 15/10, 20/10, and 25/10 cm H2O) and respiratory rates (10 and 20 breaths/min) and found that there was progressive increase in aerosol delivery with increase in inspiratory and expiratory pressures. Also, the respiratory rate of 20 breaths per minute resulted in significantly higher aerosol delivery.[139]

Vibrating mesh nebulizers were found to be more effective than jet nebulizers in improving Borg scores ($p<0.0006$), respiratory rate ($p<0.0003$) and forced vital capacity (400 ml vs 110 ml).[140] Recently, Galindo-Filho et al[130] compared jet and mesh nebulized aerosol lung delivery efficiency during BiPAP in healthy adult volunteers. The VMN (positioned next to the mask) was shown to provide a lung delivery efficiency of 5.5% (standard deviation; SD = 0.9) of the loaded dose vs. 1.5% (SD = 0.6) for the jet nebulizer (positioned between the circuit leak and mask). For better drug delivery, aerosol particles must be small enough to penetrate through the upper airways but large enough to avoid being eliminated by the expiratory flow. Devices that produce aerosols with mass of less than 2 μm are more efficient for pulmonary deposition during NIV.[141]

In acute settings, oro-nasal mask is the preferable interface in patients on NIV who require nebulized drugs. In patients who do not tolerate oro-nasal or full-face masks, or have massive sputum expectoration, nasal mask may be used as the first line option.[137]

Evidence statement:

- NIV is often used in patients with acute and chronic respiratory failure and many of these cases require aerosolized medications. Currently there is no commercially available system designed specifically for inhalation therapy during NIV.
- Majority of patients receive nebulization in between NIV sessions rather than via NIV circuit. However, short term cessation of NIV may not be possible in all patients.
- Combination of NIV along with nebulized aerosol therapy is more efficacious than aerosol therapy alone as seen on spirometry data among asthmatics. Improvements were also seen based on oxygen saturation, heart rate, respiratory rate, ICU and hospital stay durations, and reduction in the dose of bronchodilators.
- Position of the nebulizer at the mask or before Y limb of double limb circuit, or between exhalation port and the lung in single limb circuit has been found to be most effective for aerosol delivery.
- There is progressive increase in aerosol delivery with increase in inspiratory and expiratory pressures in the NIV; and a respiratory rate of 20 breaths/minute resulted in significantly higher deposition compared to 10 breaths/minute.
- Vibrating mesh nebulizers were found to be more effective than jet nebulizers in improving Borg scores, respiratory rate and forced vital capacity. In the healthy subjects, VMNs delivered 2-fold more radiolabeled drugs into the respiratory tract compared to jet nebulizers.
- Oro-nasal mask is the preferable interface in patients on NIV who require nebulization and in patients with massive sputum expectoration, nasal mask may be used as an option.

Recommendations:

- Aerosol therapy is recommended to be administered via the non-invasive ventilation (NIV) circuit and not directly by cessation of NIV in all the cases since the combination of the two is more efficacious. (III A)
- Alternatively, NIV may be disconnected for short duration for aerosol therapy on a case-by-case basis, depending on the clinical condition of the patient. (III A)

- Nebulizer should be positioned at the mask or before the Y piece of double limb circuit for optimal aerosol delivery. In the case of a single limb NIV circuit, a nebulizer should be attached between the exhalation port and the lung.(III A)
- Aerosol delivery increases progressively with increase in inspiratory and expiratory pressures and a respiratory rate of 20 breaths per minute is optimal for this purpose. (III A)
- Vibrating mesh nebulizers are recommended over the jet nebulizers for use during NIV and oro-nasal mask as the preferable interface. Nasal masks may be used as an alternative in those expectorating out large quantities of sputum. (III A)

Q 11. Should there be a pre-formulated checklist or methodology to be provided to nurses, respiratory therapists or physicians providing aerosol therapy during MV?

Protocols and strategies are to be formulated through which research results can be translated effectively and efficiently into clinical practice. Recent international surveys reported that recommendations to improve aerosol delivery are not regularly respected in current practice due to insufficient knowledge and the absence of a standardized protocol.[1,2] A pre-formulated checklist for aerosol therapy helps use of the support system in proper and adequate manner, better drug delivery to the lungs and hence better treatment outcomes. It is extremely important to ensure proper pre-assessment and preparation of the patient; proper attachments; and adequate infection control practice.[142]There are no clinical studies comparing protocol vs non-protocolized therapy. Few authors have suggested that there should be a pre-formulated checklist for nurses, respiratory therapists or physicians providing aerosol therapy during MV.[2,48] A model check list is provided in Table 2.

Table 2 – Model pre-formulated checklist for aerosol therapy for mechanically ventilated patients

Particulars	Yes	No
Check patient ID (Identify the case), re-check the orders and assess the need for bronchodilator		
Proper hand wash		
Adjust ventilator settings for nebulization		
Check sedation status (indicated to adapt the patient to the ventilator/not indicated)		
Make the patient seated in an erect (if possible) or semi-recumbent position with head end elevated 20 to 30 degrees (unless contraindicated)		
Suction of endotracheal and airway secretions		
Proper placement of nebulizer in the ventilator circuit		
Add and dilute drug as per manufacturer instructions (fill volume of 4 to 6 ml)		
Switch off the heated humidifier/Remove HME from the circuit		
Check bias flow		
Check for proper aerosolization		
Ensure peak expiratory flow within limits		
Set gas flow to nebulizer (Jet) at 6 - 8 L/min and adjust ventilator volume or pressure limit to compensate for added flow		
Tap nebulizer chamber periodically until it begins to sputter		
Check residual volume in drug chamber		
Check vital parameters at end of procedure		
Return to original ventilator settings		
Adequate washing, disinfection of nebulizer, and having a dry run before storage		
Record any adverse reactions		

Evidence statement:

- There is no data available in favour or against the use of pre-formulated check lists for aerosol therapy among mechanically ventilated patients.
- Pre-formulated check list is likely to standardize the aerosol therapy for better drug delivery to the lungs and hence better treatment outcomes. Such a model check list is provided in Table 2

Recommendations:

- Use of pre-formulated check lists for aerosol therapy is recommended for mechanically ventilated patients and each hospital/ICU should develop a checklist for their own use. (UPP)
- A model pre-formulated checklist (Table 2) is recommended which may be useful and can be modified according to the existing local conditions and requirements in a particular set up. (UPP)

Q 12. What infection control practices should be followed by persons administering aerosol therapy to mechanically ventilated patients?

Aerosol delivery is an important part of optimum care of critically ill patients. Proper handling and care of aerosol devices is especially important for suitable management of these cases.[143] These devices are classified/labelled as semi-critical devices as they come in contact with the mucous membrane of the respiratory tract. As per infection prevention and control guidelines, semi-critical devices require thorough cleaning followed by high level disinfection.[144] (Several guidelines are available for disinfection of semi-critical devices such as nebulizers and accessories.[145,146] It is also important to follow the instructions provided by the manufacturer to maintain the device and prevent contamination but these are many times not compatible with the guidelines. Recommendations for infection control while using aerosol therapy in ICU are given in Table 3.[144,147,148]

(Also see the instructions given in section I and IV of these guidelines).

Evidence statement:

- Aerosol devices come in contact with respiratory mucosa and their improper care may be associated with transmission of infection in mechanically ventilated patients.
- Nebulizers and its accessories are classified under the 'semi-critical' category and hence these require thorough cleaning and high level of disinfection. Few guidelines are available for the disinfection of these devices, however, manufacturer's instructions also need to be followed.

Recommendations:

- Aerosol delivery devices are categorized as semi-critical devices, which have the potential to transmit the infection, hence it is recommended to follow infection control measures properly among the mechanically ventilated patients in the intensive care unit. (UPP)
- Measures mentioned in Table 3 for nebulization in the intensive care unit are recommended to be followed for proper conduction of the procedure and disinfection of the instrument. (UPP)

Table 3 – Instructions for infection control during aerosol therapy in ICU.

- The respiratory therapist or the health care provider should take care of cleaning and disinfection of nebulizers in ICU.
- In-line nebulizer should be removed from circuit when not in use.
- Nebulizer chambers should be rinsed with sterile water after each use to remove the residual drug. Organic debris on the attachment should be removed and it should be cleaned with an alcohol pad or 70% alcohol.
- Manufacturer's instructions should be followed for cleaning and disinfection of nebulizers. It should be cleaned, disinfected, rinsed and air dried in between the use.
- Separate devices should be used for different patients.
- Single use dosage respules should be used to prevent contamination.
- Only sterile fluids should be used for filling and cleaning of equipment.
- Use expiratory filters with valves in aerosol delivery devices.
- While using aerosolized antibiotics, change expiratory filters after every use.

(Also see section I and V of these guidelines).

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SECTION - IV (Group - D): Use of various drugs (other than bronchodilators and inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy

Abbreviations

AIDS - Acquired immunodeficiency syndrome
AM - Alveolar macrophages
AMK - Amikacin
ATD - Anti-tubercular drugs
AZLI - Aztreonam lysine
BID - Bis in die (Twice a day)
CF - Cystic Fibrosis
CFTR - Cystic Fibrosis transmembrane regulator
cm - Centimetre
CMS - Colistimethate sodium
CNS - Central nervous system
COPD - Chronic obstructive pulmonary disease
DNAse - Deoxyribonucleic acid ase
ELF - Epithelial lining fluid
ERS - European Respiratory Society
ESC - European Society of Cardiology
FEV - Forced expiratory volume
FEV_1 (FEV1) - Forced expiratory volume in one second
FVC - Forced vital capacity
g - Gram(s)
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
H (INH) - Isoniazid
HAP - Hospital acquired pneumonia

HIV - Human immunodeficiency virus
HR - Hazard ratio
HRQOL - Health-related Quality of Life
HS - Hypertonic Saline
ICS - Inhaled corticosteroids
IFN-γ - Interferon Gamma
IV - Intravenous
L/min - Litres per minute
LCI - Lung clearance index
LIS - Aerosolized Levofloxacin inhalational solution
LRTI - Lower respiratory tract infection
MAC - Mycobacterium avium complex
MDI - Metered dose inhaler
MDR - Multi-drug resistant
mg - Milligram(s)
mg/kg - Milligram(s) per Kilogram
mg/L - Milligram(s) per Litre
mg/mL - Milligram(s) per millilitre
MIC - Minimum inhibitory concentration
mL (ml) - Millilitre(s)
MRSA - Methicillin resistant Staphylococcus aureus
μ (μm) - Micron (Micrometre)
NAC - N-acetyl cysteine
NFCB - Non-Cystic Fibrosis bronchiectasis
NO - Nitric Oxide
NTM - Non-tuberculosis mycobacteria
OAD - Obstructive airway diseases
Pa - Pseudomonas aeruginosa
PAH - Pulmonary arterial hypertension
pMDI - Pressurized metered dose inhaler
PTB - Pulmonary tuberculosis
R - Rifampicin
RCT - Randomized controlled trial
rhDNAse - Recombinant human DNase
RR - Respiratory rate
SD - Standard deviation
SGRQ - Saint George respiratory questionnaire
STOP - Standardized Treatment of Pulmonary Exacerbations
TA - Tranexamic acid
TB - Tuberculosis
TIP - Tobramycin inhalational powder
TIS - Tobramycin inhalational solution
TNS - Tobramycin nebulization solution
TRIS - Treprostinil Inhalation System
UAO - Upper airway obstruction
UK - United Kingdom
UPP - Universal practice point
VAP - Ventilator-associated pneumonia
VMN - Vibrating mesh nebulizer
WHO - World Health Organization
WHO-FC - World Health Organization - Functional Class
Z - Pyrazinamide

Introduction

Aerosolized drugs have several benefits over other routes of drug administration, including quick onset of action, ability to achieve high local concentrations in lungs with lower incidence of systemic adverse effects. Delivery of aerosolized

medications typically does not cause pain to the patient; therefore, it is frequently considered a convenient method of drug delivery. Traditionally, nebulization has been used to deliver bronchodilators and steroids in order to provide quicker symptomatic relief in patients of obstructive airway disorders (bronchial asthma, COPD, etc.). In addition, nebulized drugs are also being explored for a variety of other clinical conditions. Nebulization seems to be a promising strategy for targeted antimicrobial therapy in the treatment of many lower respiratory tract infections. It may also be useful in many other patients with significant respiratory morbidities who otherwise cannot be treated or would be at risk of systemic adverse effects of the drugs.[1,2] Therefore, nebulization is gaining popularity as an alternative mode of treatment for many difficult-to-treat conditions, and the awareness regarding its uses in conditions other than obstructive airway disorders is rapidly increasing[3] Some of its uses in conditions other than in patients with OADs have been discussed in this chapter.

Structural lung diseases: cystic fibrosis (CF) and NON-CF bronchiectasis

Structural lung diseases are typically characterized by the presence of chronic bacterial infection, chronic inflammation, and impaired muco-ciliary clearance leading to structural lung damage. Airways of patients with structural lung diseases (CF, Bronchiectasis) are often chronically infected with a variety of microbes which are often very difficult to eradicate and lead to repeated worsening in patients' symptoms, progressive deterioration in lung functions and poor quality of life. Patients with structural lung diseases also experience serious difficulty in expectorating mucus, which may be thick and purulent. Impacted and inspissated secretions may lead to superadded infections and exacerbations. Mucolytics have been used very often as an adjunct in the management paradigm to help in clearing secretions and mucus.

Cystic Fibrosis (CF)

Cystic Fibrosis (CF) is an autosomal recessive inheritable condition principally involving lungs, pancreas, liver and intestines. Pulmonary involvement characterized by chronic airway inflammation and lung infections starting at an early age, is the primary cause of premature death[4] Numerous studies now provide compelling evidence that the airways of persons with CF may be inhabited by diverse bacterial communities composed of dozens of species. Younger children (usually <5 years) are most frequently infected with Staphylococcus aureus (S. aureus) and Haemophilus influenzae (H. influenza). Observations suggest that after an initial increase during childhood, airway bacterial diversity peaks in young adulthood and then declines with advancing age and disease progression.

Despite this dramatic decrease in diversity, total bacterial density appears to remain rather constant (Fig. 1).

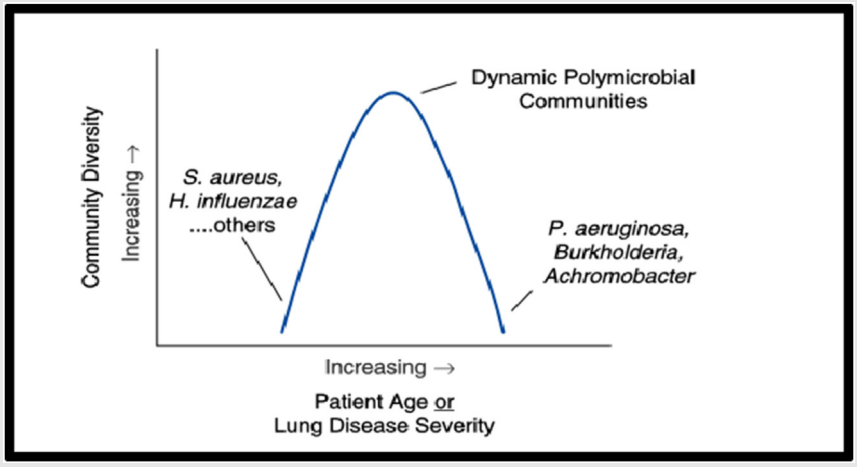

Fig. 1 – Airway bacterial community diversity versus patient age or lung disease severity in patients of Cystic fibrosis. After initial increase during childhood, airway bacterial diversity peaks in young adulthood, declines with advancing age and lung disease progression with bacterial communities dominated by a single species at end-stages. (Reference [5,6]).

Antibiotic use may be the primary driver of decreasing bacterial diversity with advancing disease. Eventually, a single species representing one of the traditional CF pathogens such as S. aureus, Pseudomonas aeruginosa (Pa), Burkholderia cepacia (B. cepacia) complex; or Achromobacter species, dominate the community.[5,6] Pseudomonas aeruginosa (Pa), B. cepacia complex, S. maltophilia are found in the environment and consequently develop ways of surviving in harsh milieus with exposure to naturally occurring antimicrobials. Treatment is difficult due to their impressive array of antimicrobial resistance mechanisms, including efflux pumps, chromosomally encoded b-lactamases, decreased outer membrane permeability, and biofilm formation.[6]

Pseudomonas aeruginosa (Pa) is one of the most common and clinically important pathogens in these patients[7,8,9] Chronic Pa colonization in CF patients (80% by adulthood) is associated with increased morbidity and mortality. Various definitions and criteria related to Pa colonization and infection are mentioned in Table 1.

Table 1 – Different definitions of (chronic) p. Aeruginosa colonization/infection (adapted from reference [9]).

European consensus criteria	
Lung colonization by Pa:	"Presence of Pa in the bronchial tree without direct (inflammation, fever, etc.) or indirect (specific antibody response) signs of infection and tissue damage"
Chronic lung colonization by Pa:	"Presence of Pa in the bronchial tree for at least 6 months, based on at least three positive cultures with at least one month intervals between them without direct (inflammation, fever, etc.) or indirect (specific antibody response) signs of infection and tissue damage".
Lung infection by Pa:	"Presence of Pa in the bronchial tree with direct (inflammation, fever, etc.) or indirect (specific antibody response) signs of infection and tissue damage. Infection can also be diagnosed on the basis of a positive antibody response in at least two examinations for patients who do not expectorate and present with negative bacterial cultures".
Chronic lung infection by Pa:	"Presence of Pa in the bronchial tree for at least 6 months, based on at least three positive cultures with at least one month intervals between them with direct (inflammation, fever, etc.) or indirect (specific antibody response) signs of infection and tissue damage. Chronic infection can also be diagnosed on the basis of a positive antibody response in at least two examinations for patients who do not expectorate and present with negative bacterial cultures."
The Leeds criteria	
Never infected by Pa:	Pa has never been cultured from sputum or cough swab.
Free of Pa infection:	No growth of Pa during the previous 12 months, having previously been Pa culture positive.
Intermittently infected by Pa:	When ≤50% of months, when samples had been taken, Pa cultures are positive.
Chronically infected by Pa:	When >50% of months when samples had been taken, Pa cultures are positive.
The Copenhagen criteria	
Chronic Pa infection:	"Persistent presence of Pa for at least 6 consecutive months, or less when combined with the presence of two or more Pa precipitins".
Intermittent Pa colonization:	"Culture of Pa at least once and the presence of normal levels of precipitating antibodies against Pa".

Pa strains causing early infection are usually antibiotic sensitive and have low bacterial density in the airways. After a first ever colonization episode, patients may go through different episodes of colonization (intermittent colonization), preceding chronic colonization by months to years, eventually resulting in chronic infection. For Pa (being the most commonly isolated chronic organism associated with long-term biofilm formation), the treatment strategy has shifted from chronic suppressive therapy in patients colonized by Pa to attempts at early eradication therapy as soon as Pa is detected[10,11] Chronic infection with methicillin resistant Staphylococcus aureus (MRSA) is also often encountered in patients with CF and is associated with increased rate of lung function decline, failure to recover lung function after a pulmonary exacerbation, and decreased survival. The easiest time to eradicate MRSA is when it is first cultured, before it becomes entrenched in the lung.[12]

Antibiotics are used for four main reasons in CF: prevention of acquisition of infection, eradication of early infection, control of chronic infection or treatment of a pulmonary exacerbation. Antibiotic choice depends on culture results, though consideration of age and likely infecting organisms is also important. The aim is to reduce bacterial load in the lungs to reduce inflammation and deterioration of lung function. Nebulized antibiotics can yield higher sputum concentrations, through direct delivery to the site of infection thereby increasing the efficiency and reducing the toxicity of systemic antibiotics. The most widely used antibiotics for nebulization at present are Tobramycin, Colistin, Aztreonam lysine and, recently Levofloxacin.[13,14]

An important issue, however, is the effect of local conditions on the clinical efficacy of antibiotic aerosol particles after deposition in the airways of patients with CF. In fact, after deposition in the airways, the local efficacy of inhaled antibiotics can be reduced by molecules within the mucus and the alginate layer surrounding the microbes like Pa[15] Inhaled antibiotics also remain unpopular for reasons like bitter taste; time taken to deliver; causing wheeze/cough. As nebulized antibiotics may cause hyperresponsiveness in sensitive airways, if patients have already been prescribed a bronchodilator, they may benefit from the inhalation of this prior to the antibiotic (or other inhaled drugs) inhalation, in order to reduce bronchospasm[9,13,14] Additional issues of relevance around the use of inhaled antibiotics in CF include cost-effectiveness, risks of adverse effects and an increase in the likelihood of acquisition of drug-resistant organisms by long-term exposure to antibiotics.[16]

Non-CF Bronchiectasis

The key components of non-CF bronchiectasis are chronic inflammation, impaired muco-ciliary clearance, chronic bacterial infection and structural lung damage[17] The common pathogens that colonize the airways of non-CF bronchiectasis are H. influenza, P. aeruginosa, S. pneumoniae, M. catarrhalis, and S. aureus[18-20] Chronic colonization, especially by Pa, has been linked to an increased risk of exacerbations, worse quality of life, and increased mortality. Isolation of Pa has been considered as an independent risk factor for accelerated decline in lung function[20-22] Chronic infection is defined when ≥3 sputum culture samples show the same pathogen at least 1 month apart in six-months. The rationale for using inhaled

antibiotics is to reduce the bacterial burden, thus breaking the vicious cycle of infection, inflammation and disease progression.[18,22]

Q1. Should nebulized antibiotics be given in the long-term management of structural lung diseases?

More than a hundred trials and articles are available on the role of nebulized antibiotics in long term-management (prevention, early eradication, and chronic suppression of pathogens) of Pa infection in CF. Many retrospective and uncontrolled studies have suggested that inhaled antibiotic therapy can prevent progression from a transient infection to a persistent or chronic infection for Pa[23-25] and leads to clinical improvement in patients with chronic Pa colonization. More recently, prospective randomized controlled trials have demonstrated the effectiveness of inhaled antibiotics, in terms of microbiological as well as clinical outcomes.[25,26]

There is still insufficient evidence to state which antibiotic strategy should be used for the eradication of early Pa infection in CF.[23] Inhaled anti-pseudomonas antibiotic probably improves lung function and reduces exacerbation rate but estimate of level of benefit was very limited. The long-term data for survival, quality of life, and nutritional outcomes are not available,[25]. Moreover, the comparison between different studies is difficult due to different methodologies, eradication treatment regimens, outcome measures and definitions of eradication and chronic colonization and/or chronic infection. The trials had low numbers of participants and short follow-up periods. Despite various flaws, most studies have supported the efficacy and tolerability of inhaled antibiotics in eradicating Pa from newly infected patients with CF and for suppression of chronic persistent Pa colonization in CF. In the case of MRSA, there is probably no role of inhaled antibiotic therapy for chronic colonization and/or eradication of MRSA in CF and future studies might help in establishing their role in maintaining a stable clinical course in CF patients.[27,28]

The evidence on the use of nebulized antibiotics in patients of non-CF bronchiectasis is still evolving.[18-21] According to a systematic review describing the use of inhaled antibiotics in subjects with stable non-CF bronchiectasis and chronic bacterial infection, inhaled antibiotics reduced the sputum bacterial load compared to placebo. The use of inhaled antibiotics also eradicated bacteria from sputum and significantly reduced the risk of acute exacerbation compared to placebo.[22]

Evidence statement:

- Inhaled antibiotics in cases of cystic fibrosis (CF) with infections of Pseudomonas aeruginosa (Pa), can prevent progression from a transient infection to a persistent or chronic infection and it can also lead to clinical improvement in patients having chronic Pa colonization. Evidence also exists regarding effectiveness of inhaled antibiotics, in terms of microbiological as well as clinical outcomes in these cases.
- Sufficient evidence is yet not available regarding antibiotic strategy for the eradication of early Pa infection in CF, however, inhaled anti-pseudomonas antibiotics probably may have a limited role. Many studies despite various flaws support the efficacy and tolerability of inhaled antibiotics in eradicating Pa from newly infected patients with CF and also for suppression of chronic persistent Pa colonization in these cases.
- There is probably no role of inhaled antibiotic therapy in the present time against chronic colonization and/or eradication of MRSA in CF.
- The role of nebulized antibiotics in patients of non-CF bronchiectasis is still evolving. These may help reduce the sputum bacterial load and reduce the risk of acute exacerbation in stable non-CF bronchiectasis and chronic bacterial infection.

Recommendations:

- Inhaled antibiotics in cases of cystic fibrosis are recommended to prevent progression of Pa from a transient infection to a persistent or chronic infection. It helps in both, microbiological as well as clinical outcomes in these cases. (IA)
- Inhaled antibiotics are also recommended, despite limitations, in eradicating early Pa infections in CF patients and inhaled anti-pseudomonas antibiotics are preferred for this purpose. (IA)
- While maintaining good standards in airway clearance, regular inhaled antibiotics should be administered for long term management of symptomatic chronic Pseudomonas infection in CF patients (IA)
- Inhaled antibiotics are not recommended for achieving early eradication or chronic suppression of MRSA infections in patients of cystic fibrosis (IIIA)
- Nebulized antibiotics may have a role in stable non-CF bronchiectasis and chronic bacterial infection in achieving early eradication, reducing bacterial load & decreasing frequency of exacerbations, but presently these are still not recommended for routine use. (IIA)
- Inhaled antibiotic therapy should not be used for prevention of airway colonization by bacteria in CF and non-CF Bronchiectasis patients (UPP)

Q2. Should nebulized antibiotics be used for acute exacerbations in structural lung diseases?

Pulmonary exacerbations in CF are when symptoms of infection become more severe. An exacerbation is defined by the European Consensus Group as the need for additional antibiotic treatment as indicated by a recent change in at least two of

the following: change in sputum volume or color; increased cough; increased malaise, fatigue or lethargy; anorexia or weight loss; increased dyspnoea; decrease in pulmonary function by >10% or radiographic changes;[29] Exacerbations have a major impact on patient quality of life and are correlated with a decline in pulmonary function. These periods of pulmonary exacerbations tend to be treated on a patient or clinician led basis, usually involving the administration of intravenous or oral antibiotics.[30]

Commonly, a combination of two antibiotics, each belonging to a different antimicrobial class are used in an attempt to enhance the efficacy of treatment, clearance of infection and prevent the emergence of antimicrobial resistance[30,31] Inhaled antibiotics have been explored either alone or in conjunction with oral antibiotics for milder exacerbations or with intravenous antibiotics for more severe infections. Practice varies among clinicians regarding the use of inhaled antibiotics in conjunction with oral and/or intravenous antibiotics.

A meta-analysis by Ryan et al[32] suggested that there is little useful evidence of quality to judge the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in people with cystic fibrosis. The trials are not sufficiently powered to achieve their goals. Thereafter, the study by Mohamed Al-Aloul et al[33] comparing 2 weeks therapy of IV Tobramycin versus 300 μg BD of Tobramycin nebulization solution (TNS) in acute exacerbations of CF patients chronically infected with Pa, concluded that TNS is effective in treating acute exacerbations due to Pa, with a renal sparing potential. A large trial, STOP (Standardized Treatment of Pulmonary Exacerbations) on 220 patients with CF exacerbations did not favor the use of inhaled antibiotics. This was attributed to the non-homogeneous distribution of inhaled medications in lungs.[34] The most recent systematic review by Smith et al[35] based on RCTs in 167 patients concluded that the available evidence is still weak on the use of inhaled antibiotics in acute exacerbations of CF due to Pa. There is no evidence regarding use of nebulized antibiotics during acute exacerbations due to organisms other than Pa.

Non-CF bronchiectasis is often characterized by repeated hospitalizations due to recurrent episodes of exacerbations. Two studies have investigated the role of inhaled antibiotics in addition to systemic antibiotics in the management of acute exacerbation of non-CF bronchiectasis.[36,37] In the multicenter study[36] involving centers in US and UK, 53 adults were randomized to receive either oral ciprofloxacin or oral ciprofloxacin and TNS. There was no difference in the clinical assessment at 14 days between the two groups. The use of TNS however resulted in greater reduction in the sputum bacterial load but with higher treatment related adverse events in the nebulized antibiotic arm. Another RCT of 143 subjects with non-CF bronchiectasis demonstrated higher sputum bacterial eradication rate with nebulized Amikacin compared to placebo. However, this study did not use clinical outcomes as the study endpoints.[37]

Evidence statement:

- The most widely used antibiotic regimen for acute exacerbations in CF comprised at least two systemic antibiotics from different antimicrobial classes without additional inhaled antibiotics.
- Inhaled antibiotics have been explored either alone or in conjunction with oral antibiotics for milder exacerbations or with intravenous antibiotics for more severe infections.
- Available evidence on the use of inhaled antibiotics during acute exacerbations of CF due to Pa is still weak, trials themselves are not sufficiently powered, some showing effectiveness of inhaled antibiotics and others not favouring them.
- There is no evidence regarding use of nebulized antibiotics during acute exacerbations of CF due to organisms other than Pa.
- In non-CF bronchiectasis also the role of inhaled antibiotics (TNS or Amikacin), in addition to systemic antibiotics, in the management of acute exacerbations, sufficient evidence is not available and are contradictory too, however, it does lead to greater reduction in the sputum bacterial load and higher sputum bacterial eradication rate.

Recommendations:

- Inhaled antibiotic as an adjunct to systemic therapy (oral/parenteral) is yet not routinely recommended in acute exacerbations caused by Pseudomonas aeruginosa in cases of cystic fibrosis (CF). (II B)
- Use of inhaled antibiotics alone is not recommended in acute exacerbations in CF caused by organisms other than Pseudomonas aeruginosa (II B)
- Role of inhaled antibiotics in addition to systemic antibiotics is yet not established in acute exacerbations occurring in cases of non-CF bronchiectasis. (II B)

Q3. Which antibiotics can be used for nebulization therapy in structural lung diseases?

Tobramycin and Aztreonam both have activity against Gram-negative bacteria that are the most common CF pathogens, in particular Pa. Each of these medications is given for 28 days followed by a 28-day drug holiday. Tobramycin is available in a dry powder inhaler (TIP) and solution for nebulization (TNS), both dosed twice daily. With regards to the evidence base for inhaled antibiotic therapy, tobramycin has been shown to be the most efficacious in significantly improving lung function,

reducing the number of exacerbations and bacterial load, and improving quality of life.[38,39] The CF Foundation has recommended chronic use of inhaled tobramycin in patients 6 years of age and older with moderate to severe lung disease and chronic Pa colonization. For patients with mild lung disease and documented persistent Pa, the use of antibiotics has moderate benefit but is still recommended.[25,26]

Aztreonam lysine (AZLI) has proven efficacy in significantly improving lung function, respiratory symptoms and, health related quality of life (HRQOL) and was well tolerated. Statistical superiority in lung function and acute exacerbations compared to TNS has also been seen. It is prescribed three times daily, which may be considered less attractive for both clinicians and patients due to adherence concerns.[40,41] Other molecules available for use include nebulized Colistin, Amikacin, Vancomycin, and Fluoroquinolones[42] Colistin products have been used as a first line approach to chronic Pa suppressive therapy for many years now. However, long-term efficacy of inhaled colistin (Colistimethate sodium; CMS) is not well documented.[43]

Although nebulized antibiotics have been available for >30 years, recent advances have focused more on dry-powder developments, with formulations currently available for Tobramycin (TIP) and Colistin. This progress has offered simple, fast and convenient delivery of inhaled antibiotics, while having similar efficacy. Inhaled liposomal Amikacin, an aminoglycoside antibiotic, with activity against Pa, has been developed for the treatment of CF respiratory infection.[44] Inhaled Fluoroquinolones, like Levofloxacin and Ciprofloxacin are also being developed. Aerosolized Levofloxacin (LIS) dose of 240 mg twice a day, is well tolerated and demonstrates significant reduction in Pa density in sputum as well as significant increase in FEV % predicted along with reduced need for other anti-pseudomonas antimicrobials[45] Recent studies support use of Ciprofloxacin DPI as a potentially more convenient alternative to nebulized antibiotic solutions for managing chronic lung infections in CF[46] Tobramycin inhalation powder (TIP) was developed to improve delivery efficiency and reduce administration time compared to TIS. The EAGER trial investigated the safety, efficacy and convenience of TIP in CF patients.[47] It concluded that TIP was easy to use and required a shorter total administration time. The safety findings observed for TIP were generally consistent with its established safety profile.[48]

The most recent meta-analyses by Smith et al[26,35] on the use of inhaled antibiotics in managing chronic infection as well as acute exacerbations in CF patients due to Pa, have concluded that no antibiotic class can be favored over the other in terms of efficacy in reducing bacterial load, patient tolerability and safety profile, as per the currently available evidence on the use of nebulized antibiotics in patients with CF. There is, however, a trend towards better patient adherence scores with the inhaled dry powder formulation over the traditionally available nebulized preparations.

There are limited numbers of studies describing the use of inhaled antibiotics in subjects with non-CF bronchiectasis.[22,49] These studies have used different antibiotics with different dosages and protocols. Most studies have described the use of nebulized antibiotics in subjects who were clinically stable and either had evidence of chronic infection or had more than 2 exacerbations in the previous year. Two studies have described the role of Aztreonam,[50] while five studies have used different formulations of ciprofloxacin.[51-55] Some of the studies have used Gentamicin in the inhaled form,[56] however, Tobramycin has been most widely used in the studies[57-60] There are many trials involving the use of nebulized Colistin as well.[61-64] The use of nebulized antibiotics was associated with increased risk of cough, dyspnoea, wheezing, dysphonia and chest tightness. The chances of respiratory adverse events were higher with the use of nebulized Tobramycin. The choice of antibiotics is mostly based on the availability and the side effect profile of the drug.

Evidence statement:

- Various nebulized antibiotics used in structural lung diseases (CF and non-CF bronchiectasis) include Tobramycin, Amikacin, Gentamicin, Aztreonam, Colistin, Vancomycin, and Fluoroquinolones.
- Although nebulized antibiotics have been used for a long time, recent focus is more towards dry-powder formulations for simple, fast and convenient delivery; while having similar efficacy in CF patients. These dry powder formulations include tobramycin, ciprofloxacin, levofloxacin, liposomal amikacin, and colistin.
- There is insufficient evidence in favour of one inhaled antibiotic over the other in managing chronic infections and acute exacerbations in CF patients in terms of efficacy in reducing bacterial load, patient tolerability and safety profile; lung functions, exacerbations, quality of life, hospitalization rates, and adverse events.
- Inhaled Tobramycin remains the most efficacious and recommended antibiotic in early eradication and chronic suppression of Pseudomonas aeruginosa infection in patients with CF. Aztreonam lysine could be another alternative but it has the disadvantage of three times dosing
- Use of inhaled antibiotics in non CF bronchiectasis has been limited and is not yet established. Tobramycin has been used more widely, however, other antibiotics used include aztreonam, ciprofloxacin, gentamicin, and colistin
- The use of nebulized antibiotics was associated with increased risk of cough, dyspnoea, wheezing, dysphonia, and chest tightness, which were more with the use of nebulized Tobramycin.

Recommendations:

- Choice of inhaled antibiotic treatment for each individual patient should be based on efficacy of the drug, infecting organism, the available nebulization system, patient characteristics & physician choices as no antibiotic has proven to be superior to others (IA)
- Inhaled antibiotics are mainly recommended for use in CF patients for early eradication and chronic suppression of Pseudomonas aeruginosa infection.(IIA)
- Tobramycin in inhaled form in cases of CF with Pseudomonas aeruginosa infection is recommended over others due to its better efficacy, easy availability and cost-effectiveness. Other alternatives include Amikacin, Gentamicin, Aztreonam, Colistin, and Fluoroquinolones (IIA)
- Dry powder inhaled antibiotic formulations in these CF cases, in recent times, are preferred over nebulized forms, because of simple, fast and convenient delivery; with similar efficacy. (IIA)
- Inhaled antibiotics are yet not recommended for routine use in cases of non CF bronchiectasis, however tobramycin may be preferred over other antibiotics (aztreonam, ciprofloxacin, gentamicin, and colistin) (IIA)
- Carefulness needs to be observed for respiratory adverse effects of nebulized antibiotics such as cough, dyspnoea, wheezing, dysphonia, and chest tightness, more so with tobramycin (IIA)

Q4. Should nebulized antibiotics be given as stand-alone therapy or as an adjunct to systemic antibiotics?

Most of the studies performed in CF patients for early eradication and chronic suppression of Pa infection have used inhaled antibiotics of different classes with or without the use of oral/intravenous antibiotics for three months period either as intermittent or continuous therapy.[26,35,65] However, there is still insufficient evidence to state which antibiotic strategy should be used for the early eradication of Pa infection in cystic fibrosis.The use of inhaled antibiotics as a stand-alone treatment for acute exacerbations in CF patients is not recommended due to erratic drug absorption as well as poor tolerability due to enhanced adverse effects.[31,35]

In case of Non-CF bronchiectasis, studies have used different antibiotics with different dosages and protocols. Many studies have described the use of nebulized antibiotics as a stand-alone therapy for chronic suppression of infection for duration of 4 weeks up to 1 year[50-54,62-64] However, during acute exacerbation two studies have investigated the role of inhaled antibiotics alone or in addition to systemic antibiotics in the management of acute exacerbation of non-CF bronchiectasis. One study used nebulized amikacin alone whereas the other used nebulized tobramycin with oral ciprofloxacin, both showing improved microbiological outcome.[36,37]

Evidence statement:

- Inhaled antibiotics of different classes with or without the use of oral/intravenous antibiotics, either as intermittent or continuous therapy have been commonly used for early eradication and chronic suppression of Pa in patients with CF. However, there is still insufficient evidence in favour of any particular strategy.
- However, their use as a stand-alone treatment during exacerbation in CF patients is not supported by the available evidence due to erratic drug absorption as well as poor tolerability.
- Role of nebulized antibiotics as a stand-alone therapy or with systemic antibiotics in non-CF bronchiectasis for chronic suppression of infection with its prolonged use or in acute exacerbation is still under study

Recommendations:

- Inhaled antibiotics can be used as standalone agents or in combination with systemic antibiotic therapy for early eradication and chronic suppression of Pseudomonas aeruginosa infection in CF patients, however, it lacks evidence as to which one of these two strategies is superior (IIB)
- Inhaled antibiotics are recommended only as add on therapy to systemic therapy whenever being used for acute exacerbations in CF (IIIA)
- Nebulized antibiotics, alone or in addition to systemic antibiotics, in non CF bronchiectasis, are still not recommended for routine use during acute exacerbation or for chronic suppression of infection. (IIA)

Q5. Should nebulized mucolytics be used in the management of structural lung diseases?

Mucolytic agents (also known as the muco-active agents) act by altering the chemical properties of airway mucus and make it easier to expel. These agents have been sub-classified as true mucolytics (drugs which make mucus thin), expectorants and muco-kinetic agents (drugs that increase mucus transport within the lungs).[66-70] Altered rheological properties of mucus and impaired clearance of mucus in the trachea-bronchial tree leads to decreased lung function, reduced quality of life and increased exacerbation rates.[67-69] The abnormal cystic fibrosis transmembrane regulator (CFTR) function results in mucus hypersecretion. The airways become vulnerable to infection and inflammation, and the influx of white cells.[71,72] These changes create an

environment favoring accumulation of altered tenacious mucus (sputum) leading to a cycle of infection, inflammation, destruction, and bronchiectasis. Inhaled mucolytic agents are designed to decrease the visco-elasticity of airway secretions, improve muco-ciliary clearance, and reduce the mucus burden in lungs of patients suffering from muco-obstructive pulmonary diseases. The commonly used inhaled mucolytics are recombinant human-DNase, mannitol, normal and hypertonic saline. Other agents such as bromhexine, erdosteine, N-acetyl cysteine have also been used but in an oral formulation.[68-70]

Inhaled mucolytics in cystic fibrosis improves quality of life, lung clearance index (LCI), lung function and reduces pulmonary exacerbations and lung function decline. The role of mucolytic agents in CF is backed by high quality systematic reviews,[73-75] RCTs,[71,72,76-83] and the consensus guidelines.[31] In patients of non-CF bronchiectasis, there are limited numbers of studies with conflicting results. Also, there is no data on the combination of inhaled mucolytics with antibiotics over and above those used as standard care. More studies with larger numbers of participants are required in non-CF bronchiectasis to further substantiate the role of inhaled mucolytics in these patients.[19,84,85]

Evidence statement:

- Altered rheological properties of mucus, its hyper secretion, and impaired clearance lead to decreased lung function, reduced quality of life and increased exacerbation rates in structural lung diseases.
- Cases of cystic fibrosis characteristically have mucus hypersecretion making them more vulnerable to infections and inflammation.
- Modest benefit has been shown with some of the inhaled mucolytic agents in CF patients in terms of reduced sputum burden and viscosity, improved muco-ciliary clearance, time to exacerbation, reduction in lung function decline, and improved quality of life. However, their role in non-CF bronchiectasis is yet not well established.
- Inhaled mucolytics seem to be a good adjunctive strategy in managing patients with structural lung diseases. Combination of inhaled mucolytics with antibiotics, though used as standard care, no data is available on this combination.
- Commonly used inhaled mucolytics include recombinant human-DNase, mannitol, normal and hypertonic saline.

Recommendations:

•Inhaled mucolytic therapy is recommended in patients with cystic fibrosis to improve the lung clearance index; prevent frequent exacerbations and lung function decline; and improve quality of life (IA)
•Presently, mucolytic therapy is not recommended in patients with non-cystic fibrosis bronchiectasis until more evidence accumulates. (IIIB)
•Mucolytics may be combined with inhaled antibiotics as part of standard care of these patients (UPP)

Q6. Which mucolytics should be preferred in management of structural lung diseases?

a) Cystic Fibrosis:

Dornase alfa is a recombinant form of the human DNase-I enzyme (rhDNAse) and digests extracellular DNA released from necrosed neutrophils. It is given as an aerosol which reduces the viscosity and surface adhesivity of sputum in CF. In a systematic review by Yang et al,[73] dornase alfa improved lung function with decreased rate of exacerbations within one month. Various studies[76,77,82,83,86-90] showed that treatment with rhDNAse resulted in improvement in lung function (increase in FEV1), decrease in incidence and severity of exacerbations, and improved quality of life. Although well tolerated, there were few adverse events that were increased by dornase alfa.

Mannitol is a sugar alcohol and used in medicine as an osmotically active agent. When inhaled it draws water into the airway by creating an osmotic gradient which has been shown to increase muco-ciliary clearance in CF.[91,92] The pooled data from studies indicated efficacy regardless of DNase use in both, improving the lung function and reducing exacerbations[75,93] Nolan et al, reported that treatment with mannitol over a 6-month period is associated with an improvement in some of the lung function in CF. However, overall, there is low quality evidence for improvement of lung function or quality of life comparing mannitol to dornase alfa alone and mannitol plus dornase alfa. The authors also found more side effects with the mannitol group.[73-75,94]

Hypertonic saline 3 % (HS) has been shown to enhance muco-ciliary clearance both in vitro and in vivo.[74,95] The strength of HS used varied between 3% and 12%, with benefits favoring more hypertonic solutions. Hypertonic saline (7%) has been shown to reduce pulmonary exacerbations and marginally improve lung function.[96] Overall, the quality of evidence for the use of HS in patients with CF is limited by the number of studies. In general, HS was well tolerated; the most common side effect was cough or bronchospasm, which was clinically significant in only a few patients.[74,76]

So far data is insufficient to recommend the routine use of nebulized NAC as a mucolytic agent in CF.[31]

Evidence statement:

- The available evidence supports the use of dornase alpha as mucolytic therapy in CF patients leading to improved lung function, decrease in incidence and severity of exacerbations, and improved quality of life, however, few adverse events may be seen.
- The use of mannitol in CF patients has been found to be efficacious in terms of improvement in lung functions and quality of life; and reduction in exacerbations, regardless of DNase use, however, side effects are more compared to DNase.
- Use of hypertonic saline (7%) has been shown to reduce pulmonary exacerbations and marginally improve the lung function and is well tolerated.
- Enough evidence for the use of nebulized N-acetyl-cysteine (NAC) as a mucolytic agent in CF patients is yet not available.

Recommendations:

- Dornase alpha is recommended as a preferred mucolytic therapy over other mucolytic agents in CF patients (IA)
- Mannitol may also be used alone or with dornase alfa in patients with CF (IIA)
- Hypertonic saline is also recommended as a good alternative for mucolytic therapy in CF patients and is preferred in a strength of seven percent (IIB)
- Nebulized N-acetyl cysteine (NAC) is yet not recommended as a mucolytic in CF (IIIA)

b) Non-Cystic Fibrosis Bronchiectasis:

Use of inhaled DNase was studied in two RCTs, with conflicting results. The first trial included 61 participants who were randomized to receive either 2.5 mg DNase twice a day or once a day or placebo over 2 weeks. There was no significant change in the outcome measures of lung function, dyspnoea and quality of life; however, there was a change in sputum transportability in vitro[97] The other larger trial included 349 participants, showed that the exacerbations and decline in lung function was more in the DNase group than in the placebo group.[98]

Mannitol has been studied in two large, randomized trials. These trials did not show any reduction in exacerbations; however, the time to the first exacerbation was longer in the mannitol group (HR 0.78, p=0.022). The Saint George respiratory questionnaire (SGRQ) score also improved in the mannitol group (-2.4 units, p=0.046).[99,100]

Normal and HS have also been studied in these cases. All the studies have been small and compared either 6% or 7% hypertonic saline to normal saline or placebo. Two studies showed a statistically significant improvement in sputum viscosity, ease of expectoration, lung function and number of annualized antibiotic courses and emergency department visits.

The latest study used a combination of hyaluronic acid and HS and showed modest benefits.[101-103] Further research is going on in this field and new mucolytic agents might be available soon. A potential target is the epithelial sodium channel, which is responsible for the composition of airway mucus by controlling sodium transport across the epithelium.[104]

Evidence statement:

- Inhaled DNase use in Non-CF bronchiectasis has shown either worsening in the form of more exacerbations or decline in lung functions or no beneficial effects. Mannitol use has also not shown encouraging results.
- Hypertonic saline (6 or 7%) has shown significant improvement in sputum viscosity, ease of expectoration, lung function, number of annualized antibiotic courses and emergency department visits in cases of Non-CF bronchiectasis. Hyaluronic acid with HS has also been used with modest results in one study.

Recommendations:

- Hypertonic saline (6 or 7%) is recommended to be used as mucolytic in non-CF bronchiectasis (IIA)
- Dornase alpha and mannitol are not recommended to be used as mucolytic agents in non-CF bronchiectasis (IIA)

Pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension is currently managed by a multi-modality approach consisting of general supportive measures, specific pharmacological treatment and surgical methods including transplantation[105] There is a great interest in delivering pharmacological treatment directly to the lungs by means of inhalation as opposed to a systemic approach in these cases.

Q7. Is there an indication for nebulized drugs in management of PAH?

There are various potential benefits of the using drugs via inhaled route in management of PAH.[106] Firstly, most of the drugs used for the treatment of PAH are vasodilators and cause systemic hypotension in addition to reduction in pulmonary vascular pressures. This can lead to unacceptable systemic adverse effects and dose limitation; these effects can be

mitigated by the inhaled route where absorption into the systemic circulation is limited. Secondly, with the inhaled route drugs are delivered to ventilated areas where their vasodilator action would lead to a decrease in ventilation perfusion mismatch and better gas exchange. On the other hand, systemically delivered vasodilators indiscriminately dilate the pulmonary arterial bed, leading to enhanced blood flow even to the poorly ventilated areas, impairing gas exchange. Third, by delivering drugs directly to the target organ, it may permit reduction of the total medication dose, potentially lowering cost. However, there are some limitations with the use of inhaled drugs as well.[105,106] Depending on the properties of the drug used, the inhalation frequency ranges from continuous use to 4 – 6 times per day, which may be impractical. The delivery systems may also be cumbersome to use. Also, control over drug dosing is less precise due to variability in breathing patterns and the difficulty in determining exactly how much medication reaches the target regions of the lung. The inhaled route has its own unique attendant adverse effects, like bronchospasm and cough, which are absent with the systemic medications. Finally, the cost might be a limiting factor.

Evidence statement:

- There is a significant potential for use of inhaled medications in Pulmonary arterial hypertension (PAH) with several benefits. But there are limitations too to these inhaled drugs which restrict their current use.
- The benefits of inhaled drugs for PAH directly reaching the target organ include no systemic hypotension and reduction in ventilation perfusion mismatch leading to better gas exchange, low dose requirement and thus a lower cost. However, these have the limitations of increased dose frequency besides erratic drug delivery to the lungs and respiratory adverse effects.

Recommendation:

- Inhaled drugs have a great potential with several benefits in the management of PAH. However, these have limited usefulness in the present time (IIB)

Q8. Which class of inhaled drugs is indicated in pulmonary arterial hypertension (PAH) and in which group of patients?

Two main classes of drugs are used via the inhaled route – nitric oxide (NO) and the prostacyclin analogues. Other inhaled drugs like vasoactive intestinal peptide, rho-kinase and tyrosine kinase inhibitors have been tried via the inhaled route in animal experiments only. Nitric oxide is an endogenous available vasodilator, used mostly for testing patients with PAH for vaso-reactivity and for pulmonary hypertensive crisis. The use of NO as an agent for treating chronic pulmonary hypertension remains under investigation.

The commonly used agents are prostacyclin analogues, namely epoprostenol, iloprost and treprostinil. Prostacyclin, an endogenous derivative of arachidonic acid in the body, has anti-proliferative, pro-apoptotic, and antithrombotic properties in addition to vasodilatation. Prostacyclin analogues are indicated in WHO functional class III and IV, i.e. advanced PAH.[105] The use of the inhaled agent depends upon its pharmacokinetic and pharmacodynamic properties.

Epoprostenol: It has noticeably short half-life (2–3 minutes) and needs to be given by continuous nebulization. Thus, it is impractical to use in the outpatient setting for treatment of chronic PAH. However, it has been used for acute pulmonary hypertension crises in critically ill patients and patients on mechanical ventilation, where it has compared favorably to NO.[107]

Iloprost: It is a prostacyclin analogue with a half-life of 7 – 8 minutes and a pharmacodynamic half-life of half an hour. It needs to be given 6 – 9 times per day. It is approved for inhalation use and is available as a proprietary inhalation device (taking up to 10 min or sometimes more) Many patients find this cumbersome and have difficulty keeping up with the recommended >6 doses/day. Inhaled iloprost is usually prescribed for out-patients with moderate-to-severe PAH who are not deemed to be sick enough and are poor candidates for or have declined infusion therapy[106] The starting dose is 2.5 μg per inhalation, which can be up titrated to 5 μg, if required[108-110] Iloprost was first approved based on the results of the Aerosolized Iloprost Randomized (AIR) Trial. This double blinded randomized control trial in 203 patients suggested that the use of inhaled iloprost for 12 weeks led to an improvement in the composite primary end point of 6-minute walk distance and functional class.[111] However, a new randomized control trial, in which inhaled iloprost was added on to bosentan, was stopped early for futility[112] The STEP study, had a similar protocol in which inhaled iloprost was added on to bosentan and showed a significant improvement in the 6 minute walk distance and WHO-functional class (WHO-FC)[113] The open label extension of the STEP study continued treatment of these patients for 12 months and found that improvement persisted[114,115] Another small study of 24 patients compared intravenous epoprostenol versus inhaled iloprost and found better response in the intravenous group.[116] Further studies are awaited in this regard.

Treprostinil: Treprostinil has the longest half-life, out of the prostacyclin analogues, viz. 3 – 4 hours. This means it can be given less frequently. It is delivered by a proprietary inhalational device. Currently, the only FDA approved nebulizer for delivery is via the Tyvaso (treprostinil) Inhalation System (TRIS) incorporating an ultrasonic nebulizer as the aerosol generator providing automatic timed actuations of the nebulized medication. It is not intended to be used during mechanical ventilation as there are currently no recommendations for selecting aerosol delivery devices for use during

mechanical ventilation. Delivery with a jet nebulizer has been reported which has its own shortcomings and VMN have also been used.[106,117,118] Vibrating Mesh Nebulizer is seen as a suitable alternative to the TRIS for inhaled treprostinil delivery, however, there are not enough published in-vitro or in-vivo studies describing its efficacy in mechanically ventilated or spontaneous breathing patients.[106]

The usual recommended upper dose limit is 54 – 72 μg per inhalation 4 times a day.[118-123] Inhaled treprostinil was approved based on the TRIUMPH study, which was a double blinded, placebo controlled randomized control trial. Treprostinil arm showed an improvement in the 6-minute walk distance and also in some secondary outcomes[118] An open label extension of the same study showed that clinical benefits were maintained in patients who continued treatment for 24 months[122] Some studies have also demonstrated that patients can be shifted from parenteral route to inhaled therapy and conversely.[116,123-129]

Evidence statement:

- Main classes of drugs for use in PAH via the inhaled route include nitric oxide (NO) and the prostacyclin analogues and all the remaining drugs are experimental only.
- The use of nitric oxide is for pulmonary hypertensive crisis only and it is still under investigation for treating chronic pulmonary hypertension.
- Commonly used agents through inhaled route are prostacyclin analogues which include - epoprostenol, iloprost and treprostinil, which are indicated in advanced PAH (WHO functional class III and IV).
- Epoprostenol has a noticeably short half-life (2–3 minutes) and needs to be given by continuous nebulization making it suitable only for acute pulmonary hypertension crises in critically ill patients and patients on MV and not for treating patients of chronic PAH in an outpatients setting.
- Iloprost has a half-life of 7 – 8 minutes and a pharmacodynamic half-life of thirty minutes requiring a cumbersome dosing of 6 – 9 times per day. It is usually prescribed for out-patients with moderate-to-severe PAH who have declined for infusion therapy. It is given by proprietary inhalation device and the starting dose is 2.5 μg per inhalation, which can be up titrated to 5 μg if required
- Inhaled iloprost has also been used with bosentan but with variable results
- Treprostinil has the longest half-life of 3 – 4 hours requiring less frequent dosing but is available only as a proprietary inhalational device incorporating ultrasonic nebulizer which is not to be used in MV patients Its use through jet and VMN has so far not been standardized either in MV or in spontaneous breathing patients.
- The usual recommended dose of treprostinil is 54 – 72 μg per inhalation 4 times a day which has shown clinical benefits in various studies.The patients on parenteral therapy can also be shifted to inhaled therapy and conversely.

Recommendations:

- Nebulized prostacyclin analogues (treprostinil and iloprost) are commonly recommended in the treatment of advanced pulmonary arterial hypertension (WHO-FC-III and FC IV). (UPP)
- Epoprostenol, another prostacyclin analogues, with a half life of 2-3 minutes, is only recommended for continuous nebulization in acute pulmonary hypertension crises in critically ill patients and those on mechanical ventilation, where it has compared favorably to nitric oxide. (II B)
- Nebulized Iloprost or Treprostinil, either of the two may be used, however, treprostinil may be preferred because of its longer half-life (II B)
- Iloprost and treprostinil are currently only used as a proprietary inhalational system and their use with regular nebulizers is not yet well standardized and hence is not recommended. (II B)
- Nitric oxide is recommended to be used for pulmonary hypertesive crisis only (UPP)

Q9. Are nebulized drugs to be given as stand-alone therapy or as adjunct to other oral drugs in PAH?

According to the ERS/ESC guidelines on PAH a sequential and systematic approach to treatment should be followed. The choice of therapy depends upon the demonstration of vaso-reactivity, functional status, availability of agents, risk category, etc. Either standalone or combination therapy may be used depending upon these factors.[105] Inhalational agents are used less commonly as they are expensive and cumbersome to use. Inhaled agents cannot be used to substitute for the infused routes of prostacyclin because they do not permit delivery of medication at high doses.

Given the limitations, inhaled iloprost and treprostinil are used less often in the PAH population compared with the oral or infused medications. Their best application appears to be for patients who are already on one or two oral agents and have not reached improvement goals but are not candidates for or have not deteriorated enough to warrant infusion therapy. These inhaled therapies would be poor choices for initial treatment of PAH because of their limited efficacy and cost, and they should not be used as substitutes for infusion therapy when needed to rescue unstable patients.

Evidence statement:

- The choice of therapy for PAH depends upon several factors such as the demonstration of vaso-reactivity, functional status, availability of agents, risk category, etc
- Nebulized drugs are best used as add-on agents in patients not controlled on one or two oral drugs, and their severity is not to such an extent to warrant infusion therapy.
- Nebulized therapies are not the choice for initial treatment of PAH for their limited efficacy and high cost and are also not the substitutes for infusion therapy in unstable patients since these cannot deliver high doses.
- Inhaled prostacyclin such as iloprost and treprostinil are used less often in the PAH population compared with the oral or infused medications.

Recommendations:

- Nebulized drugs are only recommended as an add on therapy to those who have failed to attain improvement goals with one or two oral drugs but are not the candidate for infusion therapy. (IIA)
- Nebulized drugs are not recommended for initial treatment of PAH and also not as a substitute for infusion therapy in unstable patients.(IIA)

Flexible bronchoscopy

Topical anaesthesia for flexible bronchoscopy can be achieved in several ways; administration of an anaesthetic agents through cricothyroid membrane, giving drugs through nebulization, administering the drug through oral spray or the bronchoscope by the "spray-as-you-go" technique. The most commonly used anaesthetic agent is lignocaine. The potential advantages of using nebulized lignocaine include adequate anaesthesia, better tolerance, and reduced amount of sedation during bronchoscopy, and reduced requirement for supplemental topical anaesthesia. The serious effects of lignocaine toxicity (seizures, methemoglobinemia, respiratory failure, and cardiac arrhythmias, CNS manifestations) are reported to begin at plasma levels >5 mg/L in patients with abnormal liver enzymes and at 8 mg/L in normal individuals. The concentration for topical airway anaesthesia during bronchoscopy is 1-2% lignocaine (1% lignocaine has been found to be equally efficacious as 2% lignocaine.

Q10. Is there a role of using nebulized lignocaine during flexible bronchoscopy?

It has been shown that patients treated with nebulized lignocaine received overall greater amounts of lignocaine than the placebo group. Furthermore, the administration of aerosolized lignocaine prior to bronchoscopy did not significantly improve patient comfort or prevent cough.[130,131] Although few studies demonstrated a reduction of supplemental lignocaine doses required for flexible bronchoscopy if nebulized lignocaine was previously administered, however, the small number of patients in each study did pose a question about their significance.[132] Three different methods of local anaesthesia, including nebulization, and trans-cricoid and bronchoscopic injection have been compared and the results of nebulization did not show any significant improvement above others[133] It has now been clearly established that 'spray as you go' is the better technique which provides adequate local anaesthesia to the airways and prevents lignocaine overdose.[134]

Evidence statement:

- Nebulization with lignocaine does not offer any benefit in flexible bronchoscopy over other methods and the amount of drug delivered is also more.
- 'Spray-as-you-go' is a better technique providing adequate and selective local anaesthesia to the airways and prevents overdose of lignocaine.

Recommendations:

- Routine use of nebulized lignocaine in patients undergoing flexible bronchoscopy under conscious sedation is not recommended. (IIA)
- It is recommended to use 'spray-as-you-go' technique for the local anaesthesia to the airways during flexible bronchoscopy. (IIA)

Upper airway obstruction

Upper airway obstruction (UAO) is a commonly encountered life-threatening problem in clinical practice. The presentation can be acute, insidious and even intermittent in certain cases. Although more commonly seen in children, it can be a cause of concern in certain circumstances involving adults as well. One of the most common causes of UAO is croup or acute

laryngo-tracheo-bronchitis. It has been reported that 40% of admissions with croup have features of both viral (fever, rhinorrhoea) and spasmodic (atopy, recurrence) croup. The typical clinical features are hoarseness, a barking cough, stridor and a low-grade fever.[135]

Q11. What are the indications of using nebulized drugs for management of upper airway obstruction due to Croup?

In cases of mild UAO no specific treatment is indicated. Depending on the extent of involvement of accessory muscles in the moderate croup, either 0.15 mg/kg dexamethasone or prednisolone 1 mg/kg is usually given systemically (parenteral/oral) or budesonide 2 mg in nebulized form is used. Nebulized L-adrenaline (L-epineohrine) (0.5 ml/kg of 1:1000 L-adrenaline solution) has also been recommended in more severe cases. However, for severe croup close clinical monitoring with further evaluation and follow up is required.[136] At least three studies showed that nebulized epinephrine had a statistically significant smaller croup score after 30 minutes.[137-140]

Evidence statement:

- Nebulized drugs in the form of glucocorticoids or epinephrine are useful in most cases of upper airway obstruction due moderate to severe croup as an alternative to the systemic therapy.
- Nebulized epinephrine leads to a significantly smaller croup score after 30 minutes of its administration.

Recommendations:

- Nebulized drugs belonging to the group of glucocorticoids or epinephrine are recommended to be used in the management of upper airway obstruction due to croup in moderate to severe cases as an alternative to systemic therapy (II A)

Q12. Which nebulized drugs should be used in management of Croup?

Treatment of croup with glucocorticoids is effective in improving the symptoms of croup after only 6 hours and for up to 12 hours after treatment, with significant improvement in scores of croup severity, shorter hospital stays and less use of adrenaline.[140,141] Doses of dexamethasone, administered either orally or intramuscularly, ranging from 0.15–0.6 mg/kg have been shown to be similarly efficacious for treating moderate croup. The use of single-dose oral dexamethasone treatment for mild croup demonstrates rapid symptom resolution with clinical and economic benefits.[140,142] Commonly used alternatives to dexamethasone is prednisolone (1–2 mg/kg).[142] Apart from this, use of nebulized budesonide (1-2 mg) has also shown to be effective in treating moderate croup.[143]

Inhaled L-adrenaline has also shown a temporary beneficial effect on airway obstruction in croup. It is not a definitive treatment but may allow time for the basic pathology to resolve. Normal L-adrenaline is preferred to racemic adrenaline, since it is safe, cheap and easily available worldwide.[144] Contraindications to the administration of L-epinephrine include obstructive right, left or cyanotic cardiac lesions. Simultaneous use of a nebulized steroid like budesonide improves the efficacy, since the steroid begins to work when effect of L-epinephrine decreases[145] There is no significant difference in rate of return visits or admissions following treatment with glucocorticoids compared with epinephrine. There was also no significant difference in length of stay in the hospital treated with glucocorticoids compared to those treated with epinephrine, nor were there any significant differences in the need for additional treatments.[146,147]

Evidence statement:

- Glucocorticoids in systemic (oral or parenteral) or in nebulized form and nebulized L-epinephrine are used in upper airway obstruction due to croup in moderate to severe cases. A single-dose oral glucocorticoids treatment is enough for cases of mild croup.
- Among glucocorticoids, dexamethasone orally or intramuscularly (0.15–0.6 mg/kg); or oral prednisolone (1–2 mg/kg); or nebulized budesonide (1-2 mg); or alternatively nebulized L-epinephrine in doses of (0.5 ml/kg of 1:1000 solution) can be used.
- Nebulized budesonide and L-epinephrine are equally effective, however, a combination of the two is preferred for improved efficacy since L-epinephrine has an early action and as it decreases steroids begin to work.
- Normally L-epinephrine is preferred to racemic epinephrine for being safe, cheap and easily available. Systemic steroids are also preferred over nebulized ones

Recommendations:

- Systemic steroids (oral or parenteral) are preferred over nebulized ones in acute upper airway obstruction due to croup (IIA)
- Nebulized epinephrine is recommended in cases of moderate to severe croup and L-epinephrine should be preferred over racemic epinephrine (IIA)

- Nebulized epinephrine and nebulized budesonide both are equally effective but a combination of the two is recommended while managing patients of croup (IIB)

Lower respiratory tract infections

Based on their efficacy in structural lung diseases (CF, non-CF bronchiectasis), inhaled antibiotic therapy is being investigated in patients with difficult-to-treat lower respiratory tract infections like hospital-acquired infections. The rational goal of an effective antimicrobial drug therapy is to produce, at the site of the infection, a concentration-time profile such that free drug concentrations equal or exceed the minimal inhibitory concentrations (MICs) for the infecting pathogen, as determined in vitro[13] while reducing the toxicity and development of drug resistance. The advantage of nebulized antibiotic formulations is that higher concentrations in the respiratory tract can be rapidly achieved while minimizing systemic exposure that may lead to adverse effects. Nebulized antibiotics have been used both for approved indications as well as 'off-label' uses which may include indications such as ventilator-associated pneumonia (VAP), hospital-acquired infections, and infective pulmonary exacerbations of chronic respiratory diseases.[148]

Q13. Should nebulized antibiotics be used in management of acute bacterial lower respiratory tract infections (LRTIs)?

Aerosolized antibiotics could improve airway inflammation & lead to improved clinical outcomes by decreasing the bacterial density in the airways & damage due to parenchymal inflammation in lungs.[13,148] Utilizing antimicrobial combinations targeting variable routes of drug delivery to combat MDR gram-negative pathogens is being increasingly encouraged and explored.[148,149] The antibiotics like Ceftazidime, Colistin, Aminoglycosides, Fluoroquinolones, etc. can be administered by nebulization. Similar to Tobramycin, liposomal encapsulation of Gentamicin has also been shown to prolong the residence time, increase concentrations within the lungs, and minimize systemic absorption[150] Even for Amikacin, lung concentrations achieved via the inhalation route were >20-fold higher than those achieved by the intravenous route.[151] Surprisingly, Levofloxacin also provided the highest survival rate (100%) compared to Tobramycin (60%) and Aztreonam (20%) in models of mouse lung infection.[152] However, the penetration of nebulized antibiotics into the lung parenchyma of patients with infected lungs is largely unknown. Nebulized formulations are also expensive and often require the assistance of knowledgeable respiratory therapists. Moreover, there is always a concern regarding increase in development of drug resistance.[13]

Although high-quality efficacy data are lacking, the clinicians are increasingly interested in using antibiotic nebulization. A recent systematic review analysis[153] in 672 patients treated for hospital acquired pneumonia (HAP), suggested that patients treated with intravenous and nebulized Colistin showed a higher rate of pathogen eradication and lower all-cause mortality. Nephrotoxicity did not differ significantly between the two groups. The overall quality of evidence is low, due to its imprecision and unclear results for most of the studies. Most of the use of inhaled antibiotics has been in structural lung diseases or HAP (VAP). There is minimal evidence on their use in acute community acquired pneumonia and bacterial lung abscess.[154,155]

Evidence statement:

- The antibiotics that can be administered by nebulization include Ceftazidime, Colistin, Aminoglycosides (Tobramycin, Amikacin, Gentamicin); Fluoroquinolones (Levofloxacin), Aztreonam etc.
- Nebulized antibiotics have consistently demonstrated intrapulmonary concentrations several folds higher than those achieved after parenteral administration, thus having a great potential for use against multi drug resistant (MDR) gram-negative pathogens.
- Liposomal encapsulation of aminoglycosides can further prolong the residence time and increase concentrations within the lungs, minimizing systemic absorption.
- However, there is not enough evidence in support or against the use of nebulized antibiotics for acute bacterial lower respiratory tract infections including acute pneumonia, lung abscess, etc.
- To bring inhaled antimicrobials into clinical use in patients with acute LRTIs, further studies assessing the efficacy and safety of these agents is needed.

Recommendations:

Nebulized antibiotics, in absence of high-quality efficacy data, are not yet recommended for management of patients with acute bacterial lower respiratory tract infections, acute pneumonia, and lung abscess. (IIIA).

Q14. Should nebulized anti-tubercular drugs be used in management of tuberculosis and non-tuberculous Mycobacterial infection (NTM) of lungs?

The lungs are seen as a potential portal for inhalation drug delivery in disease due to Mycobacterium tuberculosis (MTB) and Non-Tuberculous Mycobacterial (NTM) infections. The reasons are (a) targeting alveolar macrophages that harbor bacilli; (b) maintaining high drug concentrations in lung tissue and overcome the drug resistance due to high MIC; (c)

potential for delivery of toxic second-line anti-TB agents; and (d) minimizing GI or systemic side effects of drugs.[156] However, no RCTs have investigated inhaled anti-tubercular drugs (ATD), but this remains a continually active area of research.[156,157] For pulmonary tuberculosis (PTB), respirable insoluble micro- and nanoparticles of rifampin and isoniazid have received the most research attention but have been limited to animal studies so far.[158,159] Liposomal forms of ATD such as Amikacin and Capreomycin have also been developed.[160,161]

Katiyar et al[162] studied the concentration of ATDs in intracellular and extracellular components in the broncho-alveolar lavage (BAL) fluid and in the serum after administration of these drugs through inhaled and oral routes in the healthy human volunteers. The dosages of ATD given through the inhaled route were low (15 mg, 30 mg, and 75 mg for isoniazid, rifampicin, and pyrazinamide respectively) whereas standard dosages were given through the oral route. Alveolar macrophages (AM) as the intracellular component and epithelial lining fluid (ELF) as extracellular components were separated from the BAL fluid taken out through bronchoscopy and concentration of these drugs were measured in them. Simultaneously blood samples were also taken at regular intervals and drug concentrations were measured in the serum. The mean concentrations of these three drugs were found to be disproportionately high in the ELF and AM in the inhaled group as against the oral group. The serum concentrations of these drugs in the inhaled group were negligible and much lower than those for the oral group. The concentration of these ATD in the lungs were much higher than the minimal inhibitory concentration (MIC) of these drugs against MTB and hence shows its great potential against this organism both against sensitive and resistant strains.

Lung diseases caused by NTM are also frequently seen and their management may often pose difficulties. In a non-randomized, uncontrolled study on NTM lung disease, nebulized non-liposomal amikacin was given along with standard therapy. It included 20 patients who were refractory to the usual treatment, and they showed response in terms of improvement in their symptoms and better microbiological outcomes. However, toxicities recorded were high and treatment had to be discontinued in one-third of these patients.[161] Several other studies have also investigated the efficacy, feasibility and toxicity of inhaled amikacin for the treatment of NTM lung diseases.[163-165] In one of the RCT by Oliver et al which included 89 patients with refractory Mycobacterium Avium Complex (MAC) disease; liposomal amikacin was added to a multidrug regimen, which showed improvement in sputum conversion and in the 6-minute-walk test as against the placebo. Systemic toxicity seen to amikacin in the study was limited.[166]

In the present time, NTM infections of the lungs in cases of CF have risen as a major complication which is difficult to diagnose, and treat. For these patients, the US Cystic Fibrosis Foundation and European Cystic Fibrosis Society, in their consensus statement have recommended a combination of oral macrolide (preferably azithromycin) with inhaled amikacin along with another 2–3 antibiotics. Support from drug susceptibility testing may be taken while making a choice of the antibiotic but it should not be a binding. Various antibiotics that have been recommended include minocycline, clofazimine, linezolid and moxifloxaci.[167]

Evidence statement:

- Inhalation therapy has great potential for the treatment of lung diseases due to Mycobacterium tuberculosis (MTB) and Non-Tuberculous Mycobacterial (NTM) infections having several inherent benefits over systemic therapy.
- Nebulized amikacin, both non-liposomal and liposomal forms, as an add on therapy, has been found to be effective and relatively safe for NTM lung diseases, including some intractable infections. Nebulized liposomal amikacin has limited systemic toxicity and is safe also compared to non-liposomal amikacin. However, further RCTs are required to evaluate the benefit:risk ratio.
- Nebulized amikacin should be considered in place of intravenous amikacin when systemic administration is impractical, contraindicated, or where long-term treatment is required.
- Nebulized amikacin, in patients of CF having NTM infection, can be combined during the continuation phase of oral macrolides, with 2–3 additional antibiotics (minocycline, clofazimine, moxifloxacin, linezolid)
- High concentrations (much higher than the MIC) of ATDs (isoniazid, rifampicin, and pyrazinamide) have been detected in the epithelial lining fluid (ELF) and alveolar macrophages (AM) in healthy human volunteers after inhalation of low dose of these drugs as compared to levels attained after standard oral dose and with negligible serum levels.
- Not enough work has been done on inhaled ATDs against MTB, in spite of its great potential, both against sensitive and resistant strains and it remains to be an active area of research. Respirable insoluble micro and nanoparticles of ATDs are also under development but are limited to animal studies.

Recommendations:

- Nebulized Amikacin is recommended in the management of difficult to treat NTM lung disease in combination with standard multidrug therapy. Liposomal forms of amikacin are preferred over non-liposomal forms for safety reasons (II B)
- Inhaled amikacin along with 2–3 additional antibiotics (minocycline, clofazimine, moxifloxacin, linezolid) has been recommended during the continuation phase of oral macrolides in cases of cystic fibrosis developing NTM infection. (I B)
- Nebulized anti-tubercular drugs are not yet to be used for the management of pulmonary tuberculosis, however, their great potential needs to be studied by further research. (UPP)

Q15. Should nebulized antiviral drugs be used in management of Viral Lower Respiratory Tract Infections (LRTI)?

Influenza, commonly known as 'flu', is more severe than the common cold. The high mutation rate of the RNA genome of this virus, combined with assortment of its multiple genomic segments, promote antigenic diversity and resistance to antiviral drugs.[168] Antiviral drugs like ribavirin can be administered as a small-particle aerosol via a mask, tent, oxygen hood or mechanical ventilator in controlled settings.[169] Among infants and young children respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract disease. Currently, the only drug for treating RSV infection is aerosolized ribavirin and most blinded trials on these patients have shown faster RSV clearance, decreased viral shedding, and shorter hospitalization stays.[169,170] Conrad, in infant patients with respiratory syncytial virus (RSV) infection treated with aerosolized ribavirin, showed prompter resolution of the illness than did untreated controls with the greatest clinical improvement occurring between first and second days of therapy with a mean treatment duration of 4.5 days. They found it safe and effective in high risk and seriously ill infants with RSV bronchiolitis and bronchopneumonia.[169] However, precautions should be taken to avoid drug exposure of pregnant healthcare workers attending patients receiving aerosolized ribavirin therapy because of its teratogenic effects seen in experimental models.[170,171] Safer drugs are needed to ensure their widespread use to treat RSV infection.

Zanamivir, an N-acetyl neuraminic acid transition state analogue, is another antiviral drug that inhibits viral neuraminidase.[172,173] However, it is only available in a dry powder form for administration to the respiratory tract using a diskhaler and its nebulized form so far is not available. Inhaled Zanamivir is potentially helpful in improving the survival outcomes in influenza treatment, both seasonal and pandemic forms.[174-176] However, it has been recommended to initiate the treatment at the earliest, preferably within 48 hours after the onset of the symptoms. Clinical trials have shown that within these treatment windows, it significantly helps to reduce the duration of illness, symptom severity and the influenza related complications.[177,178] In one of the comparative studies, inhaled Zanamivir was found to be more effective than oral Oseltamivir in reducing the symptom severity in patients of influenza.[179] However, use of Zanamivir in nebulized form, although reported, but has yet not been approved with the currently available Zanamivir molecule owing to reports of fatal adverse effects.[180]

Laninamivir, a long-acting version of Zanamivir, can be used in inhaled form, but is approved only in Japan. It has been recommended in cases of influenza A and B viruses, both for the treatment and prophylaxis and it can be given to adults and children both. A phase-II clinical trial,[181] recently, compared the safety and efficacy of inhaled Laninamivir. A single inhalation of Laninamivir has been shown to be as effective as repeated doses of Oseltamivir,[182] likely due to its long persistence in the lung. The single dose regimen shows promise to promote improved patient compliance and convenience.

Evidence statement:

- Antiviral drugs through inhaled routes may be useful in treatment of influenza, as it limits their systemic toxicity, and enough concentration can be reached by aerosolization. However, these are still not used widely.
- Aerosolized ribavirin is used in treating respiratory syncytial virus (RSV) infection of lower respiratory tract especially among infants and children, showing faster resolution of illness. However, it is important to avoid drug exposure to pregnant HCWs because of its teratogenic effects.
- Zanamivir only available in dry powder form, is efficacious in treatment of influenza, initiating therapy for maximum benefit within 48 hours of symptom onset, and has been found to be more effective than oral oseltamivir. Its nebulized form is not approved due to fatal adverse effects.
- Laninamivir is a long-acting version of Zanamivir, used in inhaled form as dry powder inhaler, for the treatment and prophylaxis of influenza A and B virus infections in both adults and children as a single dose regimen due to its long persistence in the lung. However, the drug still awaits worldwide approval and presently it is not available for nebulization.
- Use of inhaled antiviral drugs should be individualized on a case-to-case basis depending on drug availability, patients' clinical status and immune competence, cost-effectiveness, etc.

Recommendations:

- Nebulized ribavirin is recommended in treatment of respiratory syncytial virus infection of lower respiratory tract especially among infants and children. However, precautions need to be taken to prevent exposure to pregnant healthcare workers due to its teratogenic effects. (IIA)
- Currently use of inhaled Zanamivir, available as dry powder diskhaler, is recommended in treatment of patients with influenza, initiating therapy during the first 48 hours of onset of symptoms. It is more effective than oral oseltamivir, however, its use in nebulized form is not recommended. (IIB)
- Laninamivir, a long-acting version of Zanamivir, available only as inhaled dry powder (diskhaler), is recommended in influenza A and B virus infections, both for treatment and prophylaxis among adults and children. It is yet not available for nebulization therapy. (IIIB)

Q 16. Should nebulized antifungal drugs be used in management of fungal infections of lower respiratory tract (LRT)?

Pulmonary fungal infections happen to be a major cause of mortality in organ transplant patients and those with immunodeficiency states like AIDS.[183] Pneumocystis jirovecii pneumonia, a life-threatening infection, is often seen in such patients. A good number of these patients, especially those having HIV infection, may oten be intolerant to co-trimoxazole and require alternative forms of prophylaxis like nebulized Pentamidine.[184-186] Majority of these patients find it acceptable; especially those who are unable to tolerate the first-line therapies.[187-190] However, secondary infections such as herpes zoster, oral candidiasis, and influenza, are a major concern with pentamidine inhalation therapy.

Nebulized formulations of Amphotericin-B, a polyene antifungal, have been used for the prophylaxis and treatment (as an adjunctive therapy to systemic antifungal drugs) of pulmonary aspergillosis infections in AIDS and transplant patients. Amphotericin-B is available in two different forms, deoxycholate or liposomal form. Nebulized amphotericin B deoxycholate has been used to prevent invasive pulmonary aspergillosis for a long time, however, its toxicity limits the lung tissue doses which may be achieved through intravenous administration. Long-term administration of prophylaxis with Liposomal Amphotericin B has also proved to be tolerable and useful for preventing Aspergillus infection in lung transplant patients. Both forms of amphotericin were found safe and well tolerated over a large number of medication exposures[191,192] Treatment with nebulized Amphotericin-B, as an adjunct to systemic therapy, in one of the studies was tolerated without serious toxicity and may be considered in the setting of severe immunosuppression, cancer, and/or hematopoietic stem cell transplantation in patients with difficult-to-treat fungal lung disease. The type of delivery device together with variable particle size of each aerosolized Amphotericin-B formulation has been shown to impact upon the half-life and pulmonary distribution.[193-195]

Nebulized Liposomal Amphotericin B has also been successfully tried for the treatment of post-influenza pseudomembranous necrotizing bronchial aspergillosis infection in combination with IFN-γ and GM-CSF.[196]

Evidence statement:

- Nebulized antifungal drugs have been used for the prophylaxis and treatment of respiratory infections due to fungus which are commonly seen in organ transplant patients and those with immunodeficiency states.
- Nebulized pentamidine has been used in the treatment and prophylaxis of Pneumocystis jirovecii pneumonia, a life-threatening infection, in immunocompromised and organ transplant patients, especially where first line drugs like trimethoprim-sulfamethoxazole cannot be used or are contraindicated.
- Nebulized formulations of Amphotericin-B, have been used as an adjunctive therapy to systemic antifungal drugs for the prophylaxis and treatment of of pulmonary aspergillosis infections, including those difficult-to-treat, in settings of immunosuppressive states and transplant patients. Its intravenous administration to achieve desired lung tissue doses is limited by the toxicity.
- Amphotericin B is available in two forms, deoxycholate or liposomal, and both forms were found to be safe and well tolerated.
- Long-term prophylaxis with Liposomal Amphotericin B has been found to be useful and safe for preventing aspergillus infection in lung transplant patients.
- Nebulized liposomal amphotericin B in combination with IFN-γ and GM-CSF has also been successfully tried for the treatment of post-influenza pseudomembranous necrotizing bronchial aspergillosis infection.

Recommendations:

- Nebulized antifungal agents for the prophylaxis and treatment of respiratory infections due to fungal diseases are recommended to be used in the immunodeficient and organ transplant patients. (II B)
- Nebulized Pentamidine is recommended in these patients in the prophylaxis of Pneumocystis jirovecii pneumonia especially as an alternative to first line drugs. (II B)
- Nebulized amphotericin B, in deoxycholate or liposomal form, is recommended in prevention and treatment (as an adjunctive therapy); of invasive Aspergillus pneumonia in immuno-compromised and lung transplant patients with preference to its liposomal form (II B)
- Nebulized liposomal amphotericin B in combination with IFN-γ and GM-CSF also has a potential to be used in post-influenza pseudo-membranous necrotizing bronchial aspergillosis infection which needs further studies. (III B)

Palliative respiratory care

Advanced incurable lung diseases are often associated with respiratory problems which commonly are seen in the form intractable cough and dyspnoea. Many of such diseases often have a grim prognosis. This is not only true for lung cancers but also for other diseases like severe COPD, interstitial lung diseases (ILD), pulmonary hypertension (PH) and

Table 2 – Evidence for use of inhaled medications for palliative respiratory care.

Title	Type	Method	Results
OPIOIDS			
Noseda et al. Eur Respir J. 1997 Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine.	Double blinded placebo controlled randomized trial (COPD as primary diagnosis)	Nebulized morphine (2 doses) vs. 0.9% nebulized saline over 4 days -Well designed, powered, used only single doses (N=17)	1. Subjective improvement in dyspnoea over baseline on all days of nebulized morphine but no difference between treatment groups. 2. No significant objective improvement 3. No serious adverse events were reported (prickle throat, cough, bitter taste).
Coyne et al. **J Pain Symptom Manage. 2002** Nebulized fentanyl citrate improves patients' perception of breathing, respiratory rate, and oxygen saturation in dyspnoea.	Prospective Observational study	Nebulized fentanyl with incremental doses, along with use of concurrent medicines including systemic opioids (N=32)	1. A majority of patients (26 out of 32) reported subjective improvement in breathing after fentanyl 25 microgram.
Barnes at al. **Cochrane Reviews. 2016** Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness.	Systematic review	26 studies (only RCTs) but included all the trials with opioids (N=526)	Low quality evidence that shows benefit for oral or parenteral opioids to palliate breathlessness. No evidence to support the use of nebulized opioids.
Afolabi et al. **Am J Health-Syst Pharm. 2017** Nebulized opioids for the palliation of dyspnoea in terminally ill patients.	Systematic review	Based on moderate quality of evidence from 10 RCTs on nebulized morphine, fentanyl, hydromorphone, & morphine-6-glucuronide (N=181)	1. Subjective improvement in dyspnoea. 2. Most common opioids used was morphine, and doses ranged from 5 to 200 mg; most common dose of morphine used 20 mg, & most common frequency of administration was 4 hourly. 3. Bronchospasm was least with fentanyl.
FUROSEMIDE			
Newton et al. **J Pain Symptom Manage. 2008** Nebulized Furosemide for the Management of Dyspnea: Does the Evidence Support Its Use?	Literature review of 39 RCTs	Use of 20 mg of furosemide QID for nebulization	1. Furosemide relieves dyspnea if standard treatments were no longer effective. No significant reduction objective measures, including arterial blood gases, SaO2, heart rate and respiratory rate 2. Potential for ADRs not reported
Jebe et al. **BMJ Support Pall Care. 2013** Nebulized furosemide in palliation of dyspnoea in cancer: a systematic review.	Literature review	Use of 20 mg of nebulized furosemide QID in terminally ill cancer patients (N=22)	1. Limited evidence included does not show benefit of nebulized furosemide for the relief of dyspnea in advanced cancer
LIGNOCAINE			
Chong et al. **Emerg Med J. 2005** Comparison of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease.	Randomized controlled trial	Patients received either nebulized lidocaine or nebulized bronchodilator (N=127)	1. Cough severity score significantly reduced with both lidocaine and bronchodilator, with no significant difference in efficacy 2. Common mild side effects in the lidocaine group included oro-pharyngeal numbness and bitter taste, and, in the bronchodilator group were tremors and palpitation.
Lim et al. **Chest. 2013** Long-term Safety of Nebulized Lidocaine for Adults With	Retrospective Case series	Survey on patients with 5 years history of chronic intractable cough	1. 43% reported adverse events. 2. None of the events required an emergency visit, hospitalization, or antibiotic therapy. 3. Cough score

Table 2 – (*continued*)

Title	Type	Method	Results
Difficult-to-Control Chronic Cough.			improved significantly post treatment; 80% within 2 weeks.
Slaton et al. Ann Pharmacother. 2013 Evidence for Therapeutic Uses of Nebulized Lidocaine in the Treatment of Intractable Cough and Asthma.	Literature review	Based on low quality evidence; mostly in Asthma and 7 studies on intractable cough in advanced lung diseases	1. Nebulized lidocaine in intractable cough reported efficacy. 2. Nebulized lidocaine is not first-line therapy in intractable cough and asthma, but it may provide an alternative treatment option

neuromuscular disorders leading to respiratory failure. Besides the specific treatment for the main disease, these patients often require effective symptomatic treatment of these intractable symptoms. In one of the surveys, 70% of patients with advanced cancer disease suffered with dyspnoea during the last 6 weeks of their terminal illness. This symptom is quite distressing and frightening both to the patients as well as to the care providers.[197] The patient's perception of dyspnoea and its severity, besides the severity of disease, are also dependent on the speed of its onset, extent of physical activity, levels of anxiety, and their previous experience[197,198] Some of the evidences on the role of nebulized drugs for palliation of different distressing symptoms in the respiratory care have been shown in Table 2.

Q17. Is there any role of nebulized drugs in palliative respiratory care for patients?

Due to the challenges faced with oral and parenteral treatments in terminally ill patients, nebulized forms of treatment have been explored recently. Importantly, nebulization therapy can typically be done at home in such terminally ill patients, which can provide psychological comfort to the patients. Nebulized drugs (bronchodilators, local anaesthetics, mucolytics, opioids, steroids), have been used for palliation in patients with advanced lung disease including COPD, malignancies, ILD, PH etc[197-199] Most of the studies published so far, have focused on objective and possibly irrelevant functional improvements rather than validated and clinically meaningful subjective and quality of life indicators. Longitudinal studies are, however, probably difficult since their clinical condition often changes rapidly, and attrition rates are high.[200]

Evidence statement:

- Nebulized drugs have a potential role in patients with terminal respiratory illnesses, particularly with problems like dyspnoea and cough, that are difficult to palliate.
- Various nebulized drugs that can be used for palliation in the diseases like COPD, lung cancer, ILD, PH etc; include opioids, furosemide, local anaesthetics, mucolytics, bronchodilators, steroids etc; however, more research is needed to assess their efficacy, combination with other drugs, and safety. The results in published studies are mostly objective and not validated

Recommendations:

- Nebulized drugs are recommended to be used in palliative respiratory care in terminally ill patients. (III B)
- The drugs mostly used include opioids, furosemide, local anaesthetics, mucolytics, bronchodilators, steroids etc, for diseases such as malignancies, advanced lung diseases and others (III B)

Q18. Which nebulized drugs can be used as part of palliative respiratory care?

Chronic dyspnoea

The only drugs with a proven effect on end-stage dyspnoea are opioids. Opioids receptors are found in high densities in the brain stem and may exert an inhibitory influence on respiratory drive mainly mediated by 'mu' receptors. Moreover, opioids have anxiolytic properties further diminishing dyspnoea. The relation between opioids and respiration is not simple and if used inappropriately, opioids can induce respiratory depression. However, low dose oral opioids can improve breathlessness, sometimes dramatically. The use of oral opioids for the relief of dyspnoea has been extensively studied, but concern about adverse effects like constipation, sedation, and respiratory depression has resulted in reluctance to use them.

Nebulized opioids have been tried in dyspnoea resulting from complications due to an end-stage disease like malignancy.[201] Limited research has also investigated nebulized-opioids use in the management of stable COPD and other respiratory diseases, but the results are conflicting[201,202] The most common nebulized opioids are morphine, hydromorphone, and fentanyl.

There have not been not enough controlled trials on the role of opioids through nebulized route in the palliation of dyspnoea during the end-of-life period. Majority of the patients in most of the studies have already been taking either systemic opioids or systemic steroids along with nebulized opioids. A systematic review[203] concluded that there was insufficient data to conclude whether nebulized opioids are effective for chronic dyspnoea, however, the results from these

studies suggest that these are no better than nebulized normal saline. Use of some other concurrent inhaled medications was one of the major pitfalls in all these studies.[204,205] However, a recently published randomized controlled trial[206] suggested a clinically and statistically significant reduction in breathlessness during morphine nebulization and there were no adverse events related to the treatment. The overall poor quality of evidence in support of nebulized opioids for chronic dyspnoea remains a matter of concern.[207]

Nebulized furosemide could be another drug for palliation of chronic dyspnoea and its role has also been explored. There is some evidence to suggest that nebulized furosemide could be an option to use in the management of dyspnea[208,209] Although several studies have examined the effect of nebulized furosemide for the management of dyspnea, methodological limitations make it difficult to derive conclusions in its favour regarding efficacy and the therapeutic action. Further studies are needed to find out its usefulness in these cases.[210,211]

Chronic Cough

Pathological cough is often a common symptom in terminal malignant and non-malignant diseases. Wherever possible, the aim should be to reverse or ameliorate the underlying cause, combined with appropriate measures for symptomatic relief. Persistent cough can sometimes precipitate vomiting, exhaustion, chest or abdominal pain, rib fracture, syncope, and insomnia, and these problems need to be addressed. Nebulized local anaesthetics can sometimes relieve intractable unproductive cough, where no other treatment has been useful. Both lignocaine and bupivacaine have been used for this purpose, however, their comparison in terms or efficacy and toxicity has not been done. These treatments may sometimes reduce the sensitivity of the gag reflex and may cause a transitory hoarse voice.[212,213]

There are very few controlled trials on nebulized drugs like lignocaine for the management of chronic cough (in absence of a component of airway disease) during the end-of-life period[214] Most patients in all studies were on nebulized bronchodilators and mucolytics, or received concomitant oral/systemic steroids. Overall, the available evidence does not appear to preclude the use of lignocaine as a treatment option for intractable cough[215] Various study limitations, including their design, small sample size, and inconsistencies in method and adjunctive therapies, also need to be considered.

Evidence statement:

- Low dose oral opioids can improve breathlessness in end-stage disease like malignancy or COPD, but concerns about adverse effects like constipation, sedation, and respiratory depression, limit their use.
- The role of nebulized opioids for use in palliation of chronic dyspnoea during the end-of-life period is not yet established, however, there are no treatment related adverse events seen with it. Until larger long-term controlled studies are completed, their use to treat dyspnoea should be assessed on a case-by-case basis. Commonly used nebulized opioids include morphine, hydromorphone, and fentanyl.
- Nebulized furosemide for palliation of dyspnoea could be another option, however, current available evidence is unable to draw out conclusions.
- Nebulized local anaesthetics can relieve intractable unproductive cough in terminal malignant and non-malignant diseases for which no other treatment has been found effective. Nebulized lignocaine and bupivacaine have been used during the end-of-life period for this purpose. However, enough evidence is not available and more controlled studies are required to generate data to find out its usefulness.

Recommendations:

- Nebulized opioids may be recommended for palliative therapy of chronic dyspnoea in advanced diseases such as COPD and malignancy and other respiratory diseases during their terminal phase (II B)
- Nebulized furosemide could be an option but is not yet recommended for palliation of chronic dyspnoea in advanced/terminal diseases (III B)
- Use of nebulized lignocaine or bupivacaine is recommended for palliation of chronic cough common in terminal malignant and non-malignant diseases. (III B)

Q19. What is the role of nebulized tranexamic acid in controlling haemoptysis?

Many patients with tuberculosis, cancer, and other diseases involving the lungs suffer from the frequent recurrence of significant, submassive hemoptysis, which may result in hospital stays, a reduction in quality of life, and sometimes in invasive procedures, Currently, there are no widely accepted noninvasive therapeutic options. Tranexamic acid (TXA) is an anti-fibrinolytic agent (synthetic lysine analog), which reversibly binds to plasminogen. There is no consensus regarding TXA doses or routes of administration. Similarly, there is insufficient evidence on nebulized anti-fibrinolytic agent use during haemoptysis episodes. Few case studies have looked at the benefit of nebulized TXA as a noninvasive therapy in the treatment of hemoptysis. It seems to be a safe, effective, and noninvasive method for controlling, or at least temporizing, hemoptysis in select patients. It could be useful as a palliative therapy for chronic hemoptysis and as a tool in the acute stabilization of hemoptysis.[216]

Recently a double-blind RCT was conducted to study the role of nebulized TXA (500 mg thrice a day) against placebo in 47 patients admitted with haemoptysis with varied etiologies. Those patients having massive hemoptysis (>200 mL/24 h) and who were having hemodynamic or respiratory instability, were excluded. Tranexamic acid led to a significantly reduced expectorated blood volume, control starting from day 2 of admission. It was observed that control of haemoptysis in five days of treatment was more common with TXA-treated patients than in those receiving placebo (96% vs 50%; P < .0005). Mean hospital length of stay was shorter for the TXA group (5.7 ± 2.5 days vs 7.8 ± 4.6 days; P = .046), with fewer patients requiring invasive procedures such as interventional bronchoscopy or angiographic embolization to control the bleeding (0% vs 18.2%; P = .041). No side effects were noted in either group throughout the follow-up period. It was concluded that TXA inhalations can be used safely and effectively to control bleeding in patients with non-massive hemoptysis.[217]

Evidence statement:

- Many patients with lung diseases suffer from the frequent significant submassive hemoptysis, resulting in hospital stays, poor quality of life, and sometimes even invasive procedures
- Nebulized tranexamic acid (TXA), an anti-fibrinolytic agent, seems to be a safe, effective, and noninvasive method for controlling non-massive haemoptysis in select patients or as a palliative therapy.
- Nebulized TXA in doses of 500 mg thrice a day led to resolution of haemoptysis within 2 - 5 days, shorter mean hospital stay and lesser number of patients requiring invasive procedures such as interventional bronchoscopy or angiographic embolization to control the bleeding.
- Nebulized tranexamic acid, is a safe, effective, and non-invasive method for controlling non-massive haemoptysis in select patients and may be useful as a palliative therapy.

Recommendations:

- Nebulized Tranexamic acid, in a dose of 500 mg thrice daily, is recommended for control of bleeding in lung disease of varied etiology having non-massive haemoptysis. (II B)
- Nebulized Tranexamic acid helps control haemoptysis leading to shorter hospital stay and reduced requirement of interventions to control bleeding, besides being safe. (II B)

Table 3 – Commonly used doses of various drugs in nebulization form.

A.	ANTIBIOTICS	
1.	Tobramycin	300 mg BD
2.	Aztreonam	75 mg BD/TDS
3.	Colistimethate sodium	1-2 million units BD/TDS
4.	Levofloxacin	240 mg OD/BD
5.	Amikacin (liposomal)	250-500 mg OD/BD
B.	*MUCOLYTICS*	
1.	Dornase alfa (rhDNAse)	2.5 mg OD/BD
2.	Mannitol (20%)	3 ml BD/TDS
3.	Hypertonic saline (3-7%)	5 ml BD/TDS
C.	*PULMONARY VASODILATORS*	
1.	Epoprostenol	30-50 ng/kg/min as continuous nebulization; dose titration by 10 ng/kg/min every 30 minutes
2.	Iloprost	2.5 to 5 μg per inhalation; 6 – 9 times per day
3.	Treprostinil	54 – 72 μg per inhalation 4 times a day
D.	*MISCELLANEOUS*	
1.	For acute upper airway obstruction:	
	aBudesonide	0.5 mg-2 mg BD/TDS
	bL-adrenaline (1:1000)	0.5 ml/kg stat, repeat if needed
2.	For prophylaxis of invasive fungal infections (in immuno-compromised patients):	
	aPentamidine	300 mg every 4 weeks
	bLiposomal Amphotericin-B	12.5-25 mg twice weekly
3.	For intractable cough:	
	aLignocaine (2%)	2.5-5ml stat, (repeat every 4-6 hours)
	bBupivacaine (0.25%)	2.5-5 ml stat,(repeat every 6-8 hours)
4.	For palliation of dyspnoea:	

(continued on next page)

Table 3 – (*continued*)

A.	ANTIBIOTICS	
	aMorphine sulphate	20 mg stat, repeat 4 hourly (Max 100 mg 4 hourly)
	bDiamorphine	20 mg stat, repeat 4 hourly (Max 100 mg 4 hourly)
	cFentanyl	50 μgram stat, repeat 4 hourly (Max 100 μgram 4 hourly)
5.	For mild/non-massive haemoptysis:	
	aTranexamic acid	500 mg TDS

(Some of the drugs need to be diluted prior to nebulization to make a solution. Use of a preservative-free and additive-free solution is suggested for best patient tolerance. 2-4 ml of 0.9% of sodium chloride solution is the most used diluents to make a total of 4-5 ml of nebulization solution).

Use of nebulization as an alternative method of drug delivery is a rapidly growing area in patient care, in both pulmonary and nonpulmonary conditions. Currently, popular nebulized medications, like bronchodilators and steroids, provide rapid relief in many life-threatening clinical situations arising in cases of obstructive airway disease. Recent research in the nebulization field has focused attention on many other drugs, which may provide benefit to patients with diverse diseases, who otherwise cannot be properly treated or would be at a risk of systemic adverse effects of the drugs. However, It is crucial that the nebulized drugs must have proven efficacy to provide maximal clinical benefits to the patients. More research and practical experience are likely to bring many of the previously known drugs for various clinical conditions to desirable efficacious levels in nebulized form (Table 3).

Table 4 – Common adverse effects of nebulized drugs (other than bronchodilators).

1. Dry Cough
2. Chest tightness
3. Sore throat
4. Wheezing/bronchospasm
5. Dysphonia
6. Dysgeusia (altered/bitter taste)
7. Hoarseness of voice
8. Nausea
9. Headache
10. Lightheadedness or dizziness

Patients may benefit from the inhalation of a short acting bronchodilator 10-15 minutes prior to use of nebulized drugs, to reduce cough, chest tightness, wheezing or bronchospasm; especially recommended in patients with a history of obstructive airway disease.

It is important to increase awareness among the clinicians and caregivers about these drugs and their potential uses and benefits in various disease conditions. However, despite several potential benefits, nebulization therapy also has its own share of adverse drug reactions which should be kept in mind while practicing it (summarized in Table 4).

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Section – V (Group - E): Domiciliary/Home/Maintenance nebulization therapy; public and healthcare workers education

Abbreviations

A-PAP - Auto positive airway pressure
BAI - Breath-actuated inhalers
BiPAP (BPAP) - Bi-level positive airway pressure
BTS - British Thoracic Society
CFU - Colony forming units
COPD - Chronic Obstructive Pulmonary Disease
CPAP (C-PAP) - Continuous positive airway pressure
DC - Direct current
DPI - Dry powder inhalers
ERS - European Respiratory Society
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
ICS - Inhaled Corticosteroids
Kg - Kilogram
L - Litre(s)
LABA - Long acting β 2 agonist
LAMA - Long acting Muscarinic antagonist
MDI - Metered dose inhaler
min - Minute
ml - Millilitre
NTM - Nontuberculous Mycobacteria
NJH - National Jewish Health
OAD(s) - Obstructive Airway Disease(s)
PCP - Pneumocystis carinii pneumonia
PEFR - Peak expiratory flow rate
pMDI - Pressurized Metered dose inhaler
rhDNase - Recombinant human deoxyribonuclease
RSV - Respiratory Syncytial Virus
SABA - Short acting β 2 Agonist
SAMA - Short acting muscarinic antagonist
SMI - Soft mist inhalers
UPP - Universal practice point
U.S. - United States (of America)

Introduction

Inhalation therapy is the mainstay for drug delivery in the patients of obstructive airway diseases (OADs). This is administered through various devices including metered-dose inhalers (MDIs), dry powder inhalers (DPIs), breath actuated inhalers (BAIs), soft mist inhalers (SMIs) and also the nebulizers. It has been observed in several studies that some of these patients, mostly the elderly, have difficulties in using the inhalers effectively. The use of inhalational devices is challenging for the elderly people as they may have decreased manual dexterity, impaired cognition, muscle weakness or pain, poor inspiratory efforts, decreased vital capacity, incoordination with the use of inhalers despite repeated instructions, and sometimes requirement of long-term therapy due to frequent exacerbations. In such clinical scenarios' nebulizers could be a useful alternative to handheld inhalers since optimum drug delivery with these is not totally dependent on the effort of the patient. Nebulization, in addition, has the benefit of being used in the home setting, besides having usefulness in the long-term care, hospital care, and in an emergency room.

During the recent past, there have also been several advances in nebulizer technology, making them more patient friendly besides becoming more effective. Moreover, there also has been an increased availability of nebulized drug formulations including some newer drugs and their combinations. Presently, patients with chronic OADs such as asthma and COPD; and often some other diseases too; may require long-term use of nebulized drugs at home. Although bronchodilators are most frequently prescribed, other drugs such as mucolytic, anti-inflammatory, and antimicrobial agents are also widely

used. Domiciliary or home nebulization, today, is a very effective way of delivering aerosol therapy at home for the convenience of the patient for a range of respiratory conditions, however, these must be properly and judiciously used to achieve the desired targets.Various names have been used in the literature for this form of nebulization, such as, home or domiciliary or maintenance nebulization, however, we shall be using 'Home nebulization' and 'Domiciliary nebulization', both the terms interchangeably, in this section of the guidelines.

One of the important benefits of the home nebulization could be an early discharge of some of the patients from the hospital making their stay shorter, and, in some cases may even be instrumental in avoiding admission to a hospital by offering relief and sometimes during need it can even deliver bronchodilators in high doses during exacerbations. However, while planning nebulized therapy, it is also equally important to identify a specific nebulizer type for a patient for his requirements and to ensure its optimal use.

Home or domiciliary nebulization today is gradually becoming more and more common, however, enough guidance on its proper use is not yet available, highlighting the importance of educating the health care professionals, physicians, paramedical personnel, caregivers and to the patients and their relations on all the aspects of the nebulizer therapy. Many of the aspects of home nebulization have been covered in this section.

Q1. What is the aim of domiciliary/home/maintenance nebulization?

The purpose of inhalation therapy is to deliver a drug to the lungs safely and effectively to get the desired results. To achieve this aim proper selection of an inhalation device for an individual is critical. The definition of domiciliary/home/maintenance nebulization includes duration of nebulization therapy of more than or equal to 2 weeks. Some patients who are on a long-term inhalation therapy and are unable to use handheld devices effectively for any reasons may have to opt for home nebulization. Home nebulizer therapy works by transforming a dose of medication from a liquid form to a mist, which the person then inhales through a mouthpiece or mask. It is used for a variety of medical conditions and can be used to deliver many types of drugs which have already been discussed in detail in the previous sections. Home nebulization therapy does not require the person to coordinate their breathing with the machine, which makes it easier to use than other inhalation devices and thus are often recommended for people who may have difficulty using handheld inhalers, such as infants, children and older adults, candidates with comorbidities and those requiring high treatment dosages.[1,2] In addition, home nebulization therapy delivers medication more deeply into the lungs than what some people can manage with the other devices. Though handheld inhalation devices are preferred over the nebulizers, often these are not used in a correct manner. It has been seen that between 28% and 68% of patients do not use metered-dose inhalers or dry powder inhalers well enough to benefit from the prescribed medication, and 39 – 67% of nurses, doctors, and respiratory therapists are unable to adequately describe or perform critical steps for using inhalers.[3] It has been seen that almost fifty percent of the patients who are not relieved despite giving high-dose bronchodilators through MDIs or DPIs, often are benefitted by domiciliary nebulizer therapy.[4] However, all attempts must always be made, to ensure a correct technique of use of these devices before switching over to nebulized medication. However, in certain situations in the elderly and in infants, use of a nebulizer becomes mandatory for the delivery of drugs effectively through the inhaled route.

Evidence statement:

- Home nebulization should be used in a selected set of patients who are unable to use other modes of inhaled drug therapy and who need it for prolonged periods on a regular or frequent basis.
- It has been observed that 28 to 68% of patients do not use handheld devices properly; and 39 to 67% of HCW are unable to demonstrate correctly the critical steps for their proper use. All attempts must be made to ensure a correct technique to use the handheld devices properly before switching over the patients to nebulizer therapy.
- Proper selection of an inhalation device for an individual is critical to deliver a drug to the lungs safely and effectively to get the desired results.
- Nebulizer therapy does not require the person to coordinate their breathing with the machine as with the MDI, nor it requires a high inspiratory capacity as with DPI, which makes it easier to use a nebulizer than the hand held inhalation devices.
- The term domiciliary/home/maintenance nebulization is specifically used where the duration of nebulization therapy is of more than or equal to 2 weeks.

Recommendations:

- Domiciliary/home/or maintenance nebulization is recommended to safely and effectively deliver a therapeutic dose of the required drug, in a selected set of patients, who are not able to use other modes of inhaled drug therapy and need it for regular or frequent use for prolonged periods. (UPP).
- The handheld devices (MDI and DPI) have their own shortcomings especially in case of infants and elderly and nebulization therapy is recommended to overcome these problems. (III A).
- It is recommended to make all attempts to ensure a correct technique for patients to use the handheld devices properly before switching over to a nebulizer for the safe delivery of medication. (UPP)

- Patients requiring nebulization for two weeks or more are categorized under domiciliary home, or maintenance nebulization; the different terminologies used for this form of inhalation therapy. It is recommended for a variety of medical conditions and is used to deliver many types of medicines (UPP).

Q2. What are the indications of domiciliary/home/maintenance nebulization therapy?

Indications of domiciliary/home/maintenance nebulization therapy can be based on type of disease, patients' selection criteria and type of drugs to be given.

Indications based on Diseases[5-7]:

Domiciliary nebulization therapy may be required in any of the following diseases.

- COPD
- Asthma
- Cystic fibrosis
- Bronchiectasis
- Bronchiolitis
- Interstitial lung diseases
- Respiratory syncytial virus (RSV) Infection
- Pulmonary hypertension
- Intractable cough
- Palliative Care
- Others

Indications based on patient selection[2-4]

Nebulizers are mostly used to provide aerosol therapy to patients too ill, too old, or too young to use handheld devices. Various indications based on type of patients are as follows:

- Patients who can not perform correct inhalation maneuver with metered dose inhaler (MDI) and spacer with or without face mask (elderly population/paediatric population)
- Inspired vital capacity < 1.5 times the predicted tidal volume of 7 ml/kg or the inspired flow < 30 l/min, or the breath hold capacity < 4 seconds
- Recurrent episodes of airflow obstruction despite repeated instruction on MDI therapy usage
- Distressing or disabling breathlessness despite maximal therapy with inhalers
- Altered mental state
- Cognitive decline
- Dexterity issues
- Comorbidities such as arthritis, tremors, parkinsonism etc

Indications based on Drugs to be given

Home nebulization indications can also be based on the inhaled drugs to be given to a patient as mentioned below:

- Where a patient requires inhaled medications such as: short acting β 2 agonist (SABA), long acting β 2 agonist (LABA), short acting muscarinic antagonist (SAMA), long acting muscarinic antagonist (LAMA), inhaled corticosteroids (ICS) and other drugs.[8]
- When patients require high doses of drugs that cannot be delivered through handheld devices.
- Patients requiring long term maintenance of inhaled medications
- When a patient needs a drug only available in a liquid form such as recombinant human deoxyribonuclease (rhDNase), ribavirin, lignocaine etc.[8]
- Adjuvant therapy as an antibiotic to be given through nebulized route,[9] some instances are mentioned below-
  -Nebulized tobramycin in cystic fibrosi[9] and bronchiectasi.[10]
  -Nebulized amikacin in Non-Tuberculous Mycobacteria (NTM) infection.[11]
  -Nebulized pentamidine in Pneumocystis carinii/jiroveci pneumonia (PCP).[12]
  -Nebulized ribavirin

Evidence statement:

- Selection of patients for domiciliary/home/maintenance nebulization must be done properly based on several factors and indications.
- The indications to decide domiciliary nebulization in a case are based on the type of disease; patients' characteristics; and drug/drugs prescribed. Patients must properly be evaluated and assessed for the need of home nebulization therapy based on these factors.

Recommendations:

- It is recommended that the selection of domiciliary/home/maintenance nebulization is done properly based on the indications and not just arbitrarily. (UPP)
- The criteria recommended for the selection of domiciliary/home nebulization must be based on one or more of the following factors: type of disease; patient's characteristics; and drug/drugs to be nebulized. (More details in the text) (UPP).
- Several diseases and conditions demand a prolonged or frequent use of nebulization and conditions requiring high dosages that cannot be given through handheld devices (UPP).
- The selection must also consider the physical, mental, and physiological characteristics of the patient and his previous experience with an inhalation device. (UPP)
- Domiciliary nebulization criteria should also include the type of drug (drug available only in liquid form), long term maintenance treatment (Bronchodilators and corticosteroids), use as an adjunct therapy for prophylactic or therapeutic use (Antibiotics). (UPP)

Q3. What are the issues with nebulization during travel?

There is sparse data over the use of nebulizers during the travel. For air travel, most airlines allow medical equipment which are battery operated[13,14] but permission from the airline may be needed to use nebulizer during air travel.[13,14] Also, different countries have different power points and voltages, so patients will either need an adaptor, or a battery-powered portable nebulizer. Only battery powered portable nebulizers should be preferred during the travel, however, precautions need to be taken since their efficiency may be variable. Concomitant oxygen therapy and other medications may also be required as per physician's recommendations.

According to the regulations of the U.S. Transportation Security Administration; Nebulizers, C-PAPs, BiPAPs and A-PAPs are permitted to be carried, both in the 'Carry on bags' and 'Checked bags'. However, these must be removed from the carrying case and undergo X-ray screening. Face masks and tubing may remain in the case. It is always preferable to carry nebulizers in the 'carry-on-bags' to remain handy, to be used as and when required, in the event of flight delays and probable aggravations of symptoms etc.

Liquids for the nebulizers are exempt from the 3-1-1 liquids rule.[15] This rule governs as to how much of liquid drugs one can carry in their carry-on bags: where '3' stands for that each liquid must be in a container of 3.4-ounce or less; '1' that all containers must be placed inside one clear quart-sized plastic bag; and the last '1' that each passenger is allowed only one plastic bag. Thus, liquid medications are normally allowed in excess of 3.4 ounces, in reasonable quantities, for the flight in the carry-on bags. It is also not necessary to keep these liquids in a zip-top bag. However, it is important that the official at the checkpoint, at the time of screening, before the start of the process, is informed about carrying these liquid medications.

Patient should carry additional batteries for the nebulizer in case of loss or damage or getting discharged. If the patient is traveling by car, then they should look for a portable nebulizer that has a DC adapter so that they can plug it into the car's lighter socket. If the patient is traveling overseas, then he/she will need to make sure that both voltage converter and plug adapter are required if nebulizer is to be plugged in to operate.[9]

No restrictions have been cited in India for the use of nebulizers during road and railway travel.

Evidence statement:

- Medical equipment is permitted in various travel modes as per regulations in different countries. Most of the airlines allow medical equipment which are battery operated. In India, no specific restrictions are cited. Policies in the air travel may be variable with different airlines which need to be checked for nebulizers and nebulizer fluid before the travel.
- U.S. Transportation Security Administration permits to carry Nebulizers, C-PAPs, BiPAPs and A-PAPs, both in the 'Carry on bags' and 'Checked bags'. However, it is always preferable to check regulations in the country/countries of travel.
- Nebulizer and the fluid are preferably carried in the 'Carry on bags' to be available for use during need. In-flight use of nebulizer and oxygen may require prior permission/intimation.
- Nebulization fluids, during the flight, are exempt from the 3-1-1 liquids rule and are permitted in reasonable quantities, in excess of the normal permissible limit of 3.4 ounces quantities.
- Different countries have different power points and voltages hence always carry a voltage converter, plug adapter, a car socket adapter, and also additional batteries etc during any trip.
- Battery powered portable nebulizers are preferable during the travel but their performance may be variable depending on type of nebulizer requiring dose and other adjustments.
- No regulations could be cited for in country travel by car or rail

Recommendations:

- Nebulizers usually are permitted during the air travel, both in-country and international travel, however, prior intimation/permission is preferable, especially if it is to be used during the flight inside the cabin. It is also preferable to carry the nebulizer in 'Carry on bags'(UPP)

- Enquire details and regulations for the use of concomitant oxygen therapy (as per physician's recommendation), and check regulations on liquid packs of nebulization fluid, though these are exempt from 3-1-1 liquids rule and one may carry in excess of 3.4 ounces in reasonable quantities. (UPP)
- Battery operated equipment, preferably a new generation portable handheld nebulizer should be taken during any travel and one must also carry extra batteries and all accessories to charge and run the equipment. (UPP)
- For the change over to a portable nebulizer it is recommended to consult a physician about the type of equipment, instructions on its usage and modifications in drug dosages if any. (UPP)
- There are no regulations available in the country over the use of nebulizer during road and rail travel.·(UPP)

Q4. What are the patient's limitations to use nebulizer at home?

All the patients who are prescribed home nebulization therapy may not be able to use it properly due to several limitations. The correct technique of use of inhalation devices is not only important but crucial too in achieving good results of treatment. This therapy poses several challenges, especially for the young children and elderly patients, and is also linked to suboptimal health outcomes. Nebulizer use, in contrast to pMDI and DPI, has always attracted less attention and has also not been well studied. In the few studies investigating nebulizer use by patients of COPD at home, various problems have been reported which include assembling of the nebulizer equipment and gauging how long to nebulize fluids. Inadequate cleaning of equipment after use could pose another problem. Teale et. al. estimated 50% prevalence of problems with nebulizer use among elderly patients with COPD.[16]

It is very important to understand and follow the instructions given by the prescribing physician who is also required to monitor the progress in the case. Self-medication in the nebulization therapy should never be envisaged and must always be avoided unless provided with a self-management plan by the physician who needs to be informed about the progress on a regular basis otherwise it may lead to problems and complications. There is enough evidence that proper patient education through self-management in the form of written action plans, can not only reduce the morbidity but also helps curtailing the utilization of the health-service resources by asthmatic patients.[8] The decision to continue nebulization and how long to continue it, is also to be taken by the physician. He must also try to re-introduce handheld inhalers, as and when possible. It is also important to monitor the technique of use regularly and the response periodically.

Finally, adverse drug reactions, both local and systemic, though rare, also need to be watched. Patients with comorbidities, such as, diabetes and cardio-vascular diseases, especially in the elderly population, may need to be monitored for their laboratory and cardiac parameters on a regular basis.

Considering the problems related to home nebulization use, various limitations encountered during use include[5]:

- Dependency on caregivers
- Visual factors to measure drugs and pour medications correctly
- Severely impaired cognitive status
- Impaired hand eye coordination
- Mentally challenged
- Physical limitations

Patients with comorbidities such as diabetes, and cardio-vascular diseases need special care.
(Please also refer to Q No. 11 of Section II, Group B).

Evidence statement:

- Nebulizer use has always attracted less attention and has not been as well studied as pMDI and DPI.
- Several limitations may be encountered by patients during the home nebulization therapy that may be linked to suboptimal outcomes. These are more commonly seen among the elderly COPD patients.
- Comorbidities, such as diabetes and cardio-vascular diseases, need to be watched carefully and monitored for their laboratory and cardiac parameters.
- Various limitations encountered include dependency on caregivers, impaired coordination, physical limitations, mentally challenged, and severely impaired cognitive status.
- Proper instructions and education on home nebulization and proper monitoring of cases directly or through a self management plan must always be done properly by the physician.
- The duration of the nebulization therapy is to be decided by the physician

Recommendations:

- Dependency on the caregivers is a major limitation during home nebulization amongst elderly and paediatric population. Other limitations include physical disability, mentally challenged, severely impaired cognition, and impaired visual acuity. These need to be identified and addressed by the physician to avoid sub-optimal therapy (III B).

- Proper initial instructions and education of patients on home nebulization and their proper monitoring directly or through a self management plan is recommended for better results. (UPP)
- It is recommended that those with comorbidities (such as diabetes and cardio-vascular diseases), especially the elderly must be watched more carefully and they may need special attention and care. (UPP)
- Nebulization therapy, which has always had less attention compared to pMDI and DPI, is recommended to be studied more thoroughly as home nebulization is attaining more popularity. (UPP)
- Physicians have to decide the duration of nebulization therapy in individual cases (UPP)

Q 5. What are the difficulties and problems that a patient is expected to face during the use of domiciliary nebulization therapy?

Allahaddad et al[23] conducted a study in 50 patients on home nebulization therapy for COPD to evaluate various problems encountered by the patients at home. Most frequent problems identified were: a) Failure to remove the nebulizer cap and failure to ensure free movement of vaporizer head (n=33, 66%), b) Failure to hold breath for few seconds before exhaling (n=39, 78%), c) Failure to define endpoint to stop nebulization (n=39, 78%), d) Failure to disinfect the parts and to maintain and service the equipment (n=40, 80%).

In a community survey of 40 patients, 20 had one or more difficulties with the use of nebulizer and the most frequent problems encountered were - cleaning problems (n=16, 40%), filling the reservoir (n=07, 18%) and assembling the nebulizer (n=05, 13%). Elderly patients were having reliance on the caregivers for nebulization.[24]

Other problems encountered by the patients include side effects of the therapy. Godden DJ et al[24] interviewed 405 patients of COPD and asthma and their case records were reviewed. Side effects were experienced by 54% of patients in the form of tremors and eye complaints were most reported.

Evidence statement:

- During home nebulization therapy some of the problems faced by the patients include assembling the nebulizer; filling of the reservoir; failure to define endpoint to stop nebulization; failure to hold breath for few seconds before exhaling; problems related to cleaning and disinfection; and having reliance on the caregivers in elderly patients.
- The other problems include side effects of the therapy, both local and systemic, most commonly seen are tremors and eye complications.

Recommendations:

- Adequate training and instructions for proper use of nebulizer must be given properly to the patient and/or attendant/caregiver, including assembly, filling drug, end point of nebulization, cleaning, disinfection, and maintenance. (UPP)
- Side effects must be closely watched, especially in the elderly population which commonly include tremors and eye problems. Mouthpiece instead of facemask as an interface, amongst elderly, is recommended to prevent the eye complications (UPP)

Q 6. What is the frequency of assessment and monitoring of patients?

Patients should be periodically assessed for lung function test, symptom control and sense of wellbeing.[6-8] Patients should also be assessed for effectiveness of the prescribed treatment, adherence to the treatment, need for continuing nebulization and possibility of re-introducing hand held inhalers. In the first 2 weeks check the diagnosis, response and technique of use.[8] The clinicians should also look for side effects of the treatment.[7]There is not enough evidence to recommend the frequency of assessment and monitoring of patients. Therefore, the committee felt that the assessment should be done as follows: patients and caregivers to be assessed fortnightly for the first month, then monthly for 6 months, then every 6 months and thereafter as and when required.

Subjective and Objective Response Assessment

Patients should be assessed for subjective and objective response to treatment, adherence, technique and side effects. Subjective response in terms of patients' sense of wellbeing should be assessed using a 0-10 Visual Analogue Scale.[4] Objective response in terms of lung function should be assessed in the form of Spirometry. If Spirometry is not available, PEFR (Peak Expiratory Flow Rate) assessment should be done.[25]

Evidence statement:

- The diagnosis, response and technique of use of nebulizer needs to be checked during the initial two weeks of therapy
- Thereafter periodical assessment of patients is to be done in terms of effectiveness and adherence to the treatment, the technique of use, side effects to therapy, and need for continuing nebulization.
- Possibility of re-introducing hand held inhalers as and when possible should also be looked for

- The assessment must be both subjective (visual analogue scale) and objective (spirometry or alternatively peak expiratory flow rate). It has to be done fortnightly for the first month, then monthly for 6 months, then every 6 months and as and when required.

Recommendations:·

- It is recommended to re-check the diagnosis, response, and technique during the first two weeks and thereafter periodic assessment of patients be done for the treatment efficacy, side effects, adherence, and technique (III B).
- The assessments are to be done subjectively on a 0 -10 visual analogue scale (0=perfectly well; 10=extremely unwell] and objectively in the form of spirometry or alternatively by peak expiratory flow rates. (III A).
- These assessments are recommended to be done fortnightly for the first month, monthly for next 6 months, and then every 6 months and as and when required. (UPP)
- The need for continuing nebulization should also be done periodically and attempts be made to re-introduce handheld inhalation devices as and when it is possible. (III B)
- Patients and caregivers should be educated about the proper use of nebulizer designated for the patient. (UPP)

Q 7. How to clean, maintain and service the equipment at home?

Cleaning of the nebulizer chamber and tubing is to be done to remove the bacterial contamination and reduce the frequency of exacerbations in airway diseases.[17] In a community survey on 177 patients, the most common method of cleaning was found to be the use of warm soapy water (68%).[18]

Ideally, nebulizers should be cleaned after every use. As per BTS guidelines,[19] nebulizers for bronchodilator therapy should be disassembled, washed in warm water with a little detergent at least once a day and carefully dried. Nebulizers for antibiotics should be cleaned after each use in warm water with a little detergent and dried thoroughly. Durable nebulizers for antibiotics use should be boiled for 5–10 minutes in water with a little detergent after every 30 uses.

Many manufacturers of nebulizers also recommend cleaning and disinfecting the nebulizer before using it for the first time and also if the nebulizer has not been used for a long time.[6] Different types of nebulizers and their cleaning methods have been described in Table 1.[6]

Table 1 – Different Type of Nebulizers and their cleaning methods[6].

Jet Nebulizer	Ultrasonic Nebulizer	Mesh Nebulizer
-Wash all accessories, except the tubing, in warm water with mild detergent solution. -Rinse with warm water to remove detergent residue and leave to air-dry. -Wipe the outer surface of the tubing and the compressor with a clean cloth. -If there is some water in the tubing, connect it to the compressor and blow air through the tubing for a few seconds. -Change the air filter as soon as it changes colour.	-Wash all the accessories such as mouthpiece/mask, extension tube, medication cap and air filter with a mild detergent or a commercially available disinfectant. -Wipe the main body with a damp, soft cloth.	-Medication container, mesh cap, mask adapter and mouthpiece/ mask should be washed in warm soapy solution and later left to air-dry. -Do not touch/remove the mesh cap. The remaining medication in the mesh holes can be removed by nebulizing with clean water after re-assembling the unit -Wipe the main unit with aclean cloth.

As per Irish Thoracic Society clean the chamber, interface (facemask/mouthpiece) and tubing as per manufacturer's guidelines. Washing of the chamber and interface in warm soapy water should be done and then rinsing thoroughly with clean water. The chamber and mouthpiece/facemask should be air dried or pat dried with a paper towel. The nebulizer chamber should not be cleaned with a brush as this may cause damage.[7]

Storage of the nebulizer tubing, compressor[20]

Air compressor should be covered with a clean towel. The compressor should be kept on a sturdy surface that will support its weight. The storage of the compressor should not be done on the floor. The nebulizer parts should be stored in a small bag between treatments. Cleaning of the equipment should be done in a smoke-free and dust-free location, away from open windows and cleaning of the equipment should be done after house-cleaning (especially after vacuuming and dusting).

Disinfection of the nebulizer chamber and tubing

Disinfection should be carried out along with cleaning to eliminate bacterial or fungal colonization. As per Cleveland Clinic recommendations,[20] every third day, disinfection of the chamber, and mask should be done. Soak the nebulizer chamber and mouthpiece or mask in the vinegar solution (one-part vinegar and three parts water) for 20 minutes, rinse it with sterile water, and then allow the parts to be air dried thoroughly.

As per NJH (National Jewish Health) recommendations[21] and BTS (British Thoracic Society) guidelines,[19] boiling should be done for disinfection for 5-10 minutes.

According to a review of literature by Brun et al,[22] a weekly disinfection after cleaning and drying is recommended. A dishwasher could be used as an alternative for the cleaning and drying process or spraying/rinsing the parts with ethanol 70% in water followed by drying the parts to air. Ethanol is preferred over acetic acid as it is compatible with polymers used in the devices. Acetic acid has also a low bactericidal range as compared to ethanol.

Maintenance and Servicing

As per BTS guidelines,[19] the compressor should be serviced annually; at this time the filter is normally replaced on the compressor. Consumables, mouthpiece, mask and tubing should be replaced regularly at 3–6 monthly intervals.

The tubing should be checked regularly for kinking or holes as these may affect the performance of the nebulizers. For compressors with filters or compressors with tubing, these should be changed and recorded in line with manufacturer's recommendations. Changes of these items should be scheduled and recorded by the local service provider/supplier, or as per special local arrangements.[7]

The service by the supplier, local service provider or as per special local arrangements includes cleaning and checking for safety and efficiency. Cleaning of compressors prior to inspection, repair, or service should be in line with cleaning of healthcare equipment. Patients for whom nebulizers are recommended should be advised verbally and in writing of servicing arrangements.[7]

Evidence statement:

- Cleaning, disinfection, storage, maintenance, and timely servicing of the nebulizer along with its accessories, are necessary to prevent pathogen colonization and for proper functioning of the equipment.
- Cleaning of all the accessories except tubing is done with warm water, or mild detergent solution. Thereafter, they are rinsed and air dried. Outer surface of the tubing and compressor are wiped with a clean cloth. It is advised not to use a brush for cleaning which may damage the equipment. Specific instructions related to the type of nebulizer are given in Table 1.
- Nebulizers for bronchodilator therapy need to be cleaned at least once a day; and for antibiotics after each use; and boiled for 5-10 min with little detergent after every 30 uses. New nebulizers and those which have not been used for a long time should be cleaned and disinfected before use.
- The equipment should be cleaned in a smoke and dust-free location, away from open windows. Clean the equipment after house-cleaning (especially after vacuuming and dusting)
- Disinfection of mouthpiece or mask, and chamber after cleaning is done to eliminate colonization of microorganisms. A dishwasher can also be used as an alternative for cleaning and drying.
- Different organizations have recommended different methods for disinfection which include: soaking in vinegar solution (1 part vinegar and 3 parts water) for 20 minutes followed by rinsing and air drying; or spraying/rinsing in ethanol 70%; or boiling for 5-10 minutes. This should be done every 3rd day or at least every week. Ethanol is preferable over acetic acid.
- Storage of the air compressor, covered with a clean towel, is done on a sturdy surface, but not the floor. All the nebulizer parts are stored in a small bag between treatments.
- The compressor is serviced annually with replacement of the filter. Consumables, mouthpiece, mask and tubing should be replaced regularly at 3–6 monthly intervals.
- Manufacturer's instructions, wherever available, should always be followed.

Recommendations:

- Cleaning of all the accessories of nebulizer is recommended to be done with warm soap water or mild detergent solution, or by using a dishwasher; preferably after each use in case of antibiotic or after the last use of the day for bronchodilators. Thereafter, it should be air-dried and stored properly. [III A].
- Disinfection of the equipment is recommended after every 3-7 days preferably by using 70% ethanol; or soaking in acetic acid (vinegar) in water (1:3) for 20 minutes; or boiling for 5-10 minutes. Tap water should not be used. [III A]
- Always clean the equipment in a smoke and dust-free place away from open windows preferably after house-cleaning (UPP).
- Store the air compressor on a sturdy surface, not the floor, covered with a clean towel and all other parts in a bag. (UPP).
- The compressor is serviced annually with replacement of the filter. Filters should be checked monthly and changed earlier if discoloured. Consumables, mouthpiece, mask, and tubing should be replaced regularly at 3–6 monthly intervals. Manufacturer's instructions, wherever available, should be followed (UPP)

- Disposable nebulizer chambers should be replaced every 3 months while durable chambers can last up to a year if cleaned adequately [UPP].

Q8. What is the need for infection control measures with domiciliary nebulization and which measures are to be taken ?

Jarvis et al[17] conducted a study on microbial contamination of domiciliary nebulizers and its clinical implications in chronic obstructive pulmonary disease in which random microbiological assessment of domiciliary nebulizers were undertaken together with an enquiry into cleaning practices in 44 nebulizers from 37 patients. Only 3/44 nebulizers were cleaned on a regular basis and 73% were found contaminated with microorganisms at >100 colony forming units/plate. Potentially pathogenic bacteria colonized 13 of the 44 nebulizer (30%) and organisms isolated were Pseudomonas aeruginosa, Staphylococcus aureus, multidrug resistant Serratia marcescens, Escherichia coli and multi-resistant Klebsiella species, Enterobacteriaceae and fungus Fusarium oxysporum. Washing of nebulizer masks, chambers and mouthpieces achieved complete eradication of Gram-positive bacterial and fungal flora. Gram negative organisms were incompletely eradicated, which may be attributed to the presence of biofilms.

They also found that in patients with pathogenic organisms cultured on the nebulizer sets, there was a higher probability of occurrence of a COPD exacerbation with a mean number of exacerbations of 3.3 per year in the group in whom pathogens were isolated compared with 1.7 exacerbations per year in those whose sets grew non-pathogenic flora (p=0.02).

In another cross-sectional, observational, multicenter study on contamination of home nebulizers used in 77 CF patients, it was observed that despite the high frequency hygiene of the nebulizers reported, the cleaning and disinfection methods used were often inadequate[26] The frequency of nebulizer contamination found was 71.6%, which included bacterial contamination in 56.8% and fungal contamination in 45.9% of the cases. Among bacterial contaminants, Gram-negative bacteria were the commonest, comprising Pseudomonas spp. (31.0%) and *Acinetobacter* spp. (21.4%). *Staphylococcus* spp. (21.4%) and *Micrococcus* spp. (14.3%) were the most frequent Gram-positive bacterial species. *Candida* spp. was the most frequently observed fungus (52.9%). The use of tap water in cleaning methods and outdoor drying of the parts significantly increased (9-10 times) the chance of nebulizers' contamination.

Several studies which assessed contamination of the equipment and frequency of at least one pathogen reported a high rate of nebulizer contamination, around 60%.[27-33] Home nebulizer use was associated with a 28.5-fold greater chance of bacterial contamination.[34] Nebulizers might be the primary source of colonization for some patients,[33] since proper cleaning instructions are not adequately followed,[29] and therefore, instead of acting as an auxiliary tool for the treatment of CF, nebulizers can become a harmful device if not used properly.[26]

Fungal contamination is less explored in available literature and other studies have also reported contamination by yeast, specifically by *Candida albicans* (14.0%),[29,31,32] Peckham et al.[35] conducted a study to analyze specifically the fungal flora of nebulizers of CF adult patients and found a higher frequency of positivity (57.7%) than reported in the Brazilian study (45.9%).

Infection control measures are as follows: -

A weekly disinfection after washing (soap or mild detergent) and drying is recommended as rinse or spray the parts with 70% ethanol in water and dry the nebulizer parts to air.[22] Acetic acid (vinegar) in water can be used for disinfection.[20] Damp environment should be avoided, as dampness promotes bacterial contamination. The nebulizer should be run empty for a moment or two before the next use.[19]The nebulizer solution should be freshly reconstituted before every usage and the remnant solution should be discarded after use.[19] Cleaning of the equipment should be done in a smoke-free and dust-free location, away from open windows and after house-cleaning (especially after vacuuming and dusting).[20] The nebulizer chambers should not be shared.

Evidence statement:

- In practice most of the domiciliary nebulizers are not cleaned regularly and properly, and most (73%) are found contaminated with microorganisms at >100 colony forming units/plate and a substantial number (30%) have potentially pathogenic bacteria or fungus. Home nebulizer use has been found associated with a 28.5-fold greater chance of bacterial contamination.
- Organisms found to contaminate nebulizers include bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus, multidrug resistant Serratia marcescens, Escherichia coli, multi-resistant Klebsiella species, Enterobacteriaceae, *Acinetobacter species, Micrococcus species* and fungi such as Fusarium oxysporum, and Candida species. In general fungal contamination has been less explored than others
- There is a higher probability of infective COPD exacerbations (3.3 per year) in the group where pathogens were isolated in the nebulizers compared to the group where only non-pathogenic organisms were isolated (1.7 per year) and the same could be true for patients with CF as well as other patients.
- Washing of nebulizer and its accessories easily eradicates Gram-positive bacterial and fungal flora, however, Gram-negative organisms are incompletely eradicated and biofilms on some could be one of the reasons. The chances of contamination of the nebulizer are increased by 9-10 times on washing it with tap water and drying it outdoors which is significant.
- It has been said that the nebulizer drug solution should be freshly reconstituted before every usage and the remnant solution should be discarded after use. The nebulizer chambers should not be shared.

- Regular washing, drying, and disinfection of the equipment prevents colonization of microorganisms. A smoke-free, dust-free, and non-humid location be chosen for this purpose, away from open windows and after house-cleaning. Nebulizer should be run empty for a few seconds before next use.

Recommendations:

- Improper and inadequate cleaning and disinfection of home nebulizers and their accessories often leads to contamination with bacterial, both pathogenic and non pathogenic, Gram positive and Gram negative; and fungal organisms. Home nebulizers particularly have several fold greater chances of contamination. (IIIA)
- These are recommended to be regularly and properly cleaned, disinfected, and dried to avoid contamination with a wide variety of microorganisms. Gram-positive bacteria and fungal flora are easily eradicated, however, Gram-negative organisms are difficult to remove. (IIIA)
- Regular cleaning and disinfection of nebulizers prevent infections, such as infective exacerbations of COPD, cystic fibrosis, from the organisms colonized in these nebulizers. (IIIA)
- It is recommended to use only freshly reconstituted drug solution and remnant solution should be discarded after use. The nebulizer chamber should be given a dry run for a few moments before use and it should not be shared. (UPP)
- Nebulizer should be kept in a smoke, dust and moisture free environment away from open windows. Tap water should not be used for cleaning and outdoor drying of parts should be avoided (UPP)

Q9. Does education really make any difference in treatment outcome?

Compliance in inhaled therapy has always been a matter of great concern and scientists have always been looking for ways and means to improve it. Education of the patient and their caregiver's could have a great role in improving it. Corden et al conducted a study on patient's compliance with treatment and its relation to the quality of life and included 93 patients of COPD receiving home nebulization. Data was compiled in 82 cases and they could find treatment compliance in 36 cases (44%) and the remaining 46 (56%) were poorly compliant. The compliance was found to have a negative correlation with the total score on the St George Respiratory Questionnaire ($p=0.03$) indicating that better compliance is linked with better quality of life. This indicates that educating patients and or their caregiver may have a positive impact on treatment outcome.[36]

Another study by Melani et al[37] in 1257 patients on home nebulization found that educating a patient or caregiver improved the cleaning and maintenance practices of nebulizers.

Other studies have also proved that a patient or caregiver faces several problems while managing nebulization at home[23,38,39] and educating them may solve the difficulties encountered and better results of therapy. Monitored nebulization therapy always improves the treatment outcome.[4,40] European Respiratory Society (ERS) and British Thoracic Society (BTS) have emphasised on the education of the patient (or caregiver) to improve efficacy of treatment and minimizing the wastage of drug.[18,19]

Evidence statement:

- Patients or caregivers face several difficulties related to the management of domiciliary nebulization.
- Education related to nebulization therapy to the patient and/or caregiver, improves compliance, efficacy, quality of life and the outcome; minimizes wastage of drug; and improves the cleaning and maintenance of the equipment.

Recommendations:

- Patient and/or caregivers education is a very important component of home nebulization programs. (UPP)
- It is recommended that the patient and caregiver should be properly educated about the domiciliary nebulization which improves treatment compliance, efficacy, quality of life and outcome; minimizes drug wastage; with better cleaning and maintenance of the equipment (III A).

Q10. Who should take the responsibility of educating the public and health care workers?

There is a lack of literature regarding who should take the responsibility to educate the patients regarding home nebulization.

There are studies[41,42] and meta-analysis[43] that proved that untrained nurses or inexperienced doctors cannot do the job of educating patients regarding inhaler technique (MDI, & DPI) successfully. Both BTS[19] and ERS[8] recommend that there should be "inhaled therapy coordinator" as per local needs and doctor, nurse or physiotherapist can be a part of this but that person should have adequate knowledge and experience regarding nebulization therapy.

Inhaler therapy coordinator should provide education to other healthcare professionals and patients in addition to running an assessment and support service for patients. In addition, there should be an instruction manual along with each nebulizer machine for the proper use of the nebulizer system.

Evidence statement:

- Previous experience with untrained nurses or inexperienced doctors in educating patients regarding MDI and DPI inhaler techniques has been poor and they were not found suitable for this task.
- An "Inhaled therapy coordinator" has been recommended by BTS and ERS to take up this responsibility and doctors, nurses or physiotherapists with adequate knowledge and experience in nebulization therapy can be assigned this job. They should also provide education to other healthcare professionals, patients and caregivers.
- The "Inhaled therapy coordinator", besides education, should also provide an assessment and support service for patients at their home to improve proper usage and compliance.
- Nebulizer at the time of purchase must accompany an instruction manual for proper usage of the machine.

Recommendations:

- Untrained health care professionals should not be assigned the job of educating and training the use of nebulization therapy (IIIA)
- Doctors, nurses, and health care professionals (HCP) with adequate knowledge in nebulization therapy are recommended to be given the responsibility as 'Inhaled therapy coordinator' and assigned the task to educate other HCPs, patients, and caregivers. (UPP)
- It is also recommended that 'Inhaled therapy coordinator' should provide an assessment and support service for patients at their home for the optimal utilization of nebulization therapy (UPP)
- Manufacturer must also provide an instruction manual for proper use of a nebulizer at the time of purchase. (UPP)

Q11. Whom to educate for home/domiciliary/maintenance nebulization?

Both, ERS[8] and BTS[19] focus on the proper education of the patient for nebulization therapy. For children below the age of understanding, patients of low IQ, debilitating patients, educating the caregiver will provide maximum benefit to the patient. Caregivers may be chosen from among the family members or they could also be professional healthcare personnel. Till date there exists no agreed standard for caregivers and no guideline for them as well. People usually focus on patient health mainly and are not concerned about the health of the caregiver. There are several issues with the caregiver which also need to be addressed. Studies have shown that caregivers often suffer a gradual health breakdown, depression, and mental stress which need to be properly addressd since these are likely to affect the patient's health.[44-47]

Evidence statement:

- Focus of education on home nebulization therapy should be on the patient who has the capability to be trained; and in case of young children, patients of low IQ, debilitating patients; caregivers need to be educated for proper delivery of the therapy.
- There is no definite guidance for selection of a caregiver, however, this may be a family member or a professional health care personnel having good physical and mental health. Caregivers have been found to suffer from a gradual health breakdown, depression, and mental stress which is likely to impact a patient's health.

Recommendations:

- The emphasis of education on home nebulization is recommended primarily to be on the patient, and in case he or she is not found suitable physically or mentally, it should be on the caregiver. (UPP)
- A caregiver, in good physical and mental health, with a good understanding, is recommended to be chosen amongst the family members or alternatively may be a professional health care personnel. (UPP)
- Health related issues of the caregiver must also be addressed properly. (UPP)

Q12. What are the follow-up timings for patient's education (frequency of education)?

There are no existing recommendations on this issue. For maximum compliance the follow up timings of the patient's education should match the timings of assessment and monitoring, as mentioned previously. This is likely to be more convenient and practical.

Evidence statement:

- There are no recommendations in the literature about the follow up timings for the patient education. This should be at regular intervals, matched with the patients' follow up visits, which may improve patients' adherence and compliance.

Recommendations:

- The timings of a patient's education are recommended to be at the time of assessment and monitoring of the patient, that is, fortnightly for the first month, monthly for the next 6 months, and then six monthly and also as when required in between.(UPP)

Q13. What are the topics for education to be focused for patients, caregivers and health care workers?

Structured training modules need to be formulated for patients and caregivers; health care workers; and doctors, to have a uniform education pattern for every category and these modules can be modified according to the local requirements.

Topics for Structured Training Module for the Patients and Caregivers[19] *include: -*

- Different nebulizer systems, its parts, how to assemble and disassemble them
- Prescribed drugs, dosages, frequency, and how to fill the chamber
- How to prepare the drug solution and what precautions are to be taken. Mixing of drugs and diluents is not to be done unless advised by the physician.
- Steps to nebulization and their proper technique
- Duration of nebulization, what is the endpoint, and the residual volume
- Difficulties and problems faced during the use of domiciliary nebulization therapy
- Oxygen driven nebulizer to be used only if advised, not otherwise, and precautions for its use
- Side effects of the therapy, both local and systemic; warning signs and remedies
- Instructions during travel
- Cleaning, drying, disinfection, storage; regular servicing and maintenance of the nebulizer. Emphasis on the need for infection control measures.
- About interfaces, how to choose and use
- Special precautions among the elderly population
- Emergency action plan for acute exacerbation
- Importance of monitoring and follow up
- Special precautions during nebulization of patients or suspects of the COVID-19 or other contagious infections

Topics for Structured Training Module for the Health care workers[19] *include: -*

- Details of various inhalation devices and their proper use
- Aim and principle of nebulization and its domiciliary use
- Various types of nebulizers, their parts, comparison, and functionalities
- Various drugs for nebulization, their dosages and frequency. and how to fill the chamber.
- How to prepare the drug solution and what precautions are to be taken.
- Issues related to mixing of drugs and adding diluents to the solution.
- Steps to nebulization and its proper technique (method of inhalation, adequate gas flow rate, fill volume, duration, use of filter)
- Duration of nebulization, what is the endpoint, and the residual volume
- Difficulties and problems faced during the use of domiciliary nebulization therapy
- Driving gas in the nebulizers and when and where to use oxygen driven nebuliser and precautions to be taken
- Side effects of the therapy, both local and systemic; warning sign and remedies
- Cleaning, disinfection, drying, and storage; regular servicing, and long-term maintenance. Emphasise the need for infection control measures.
- Regular monitoring and assessment of the patient during the follow up
- Emergency action plan for acute exacerbation
- Instructions during travel
- Precautions to be taken while changing from less efficient jet to highly efficient vibrating mesh nebulizer such as adjustments of dosages
- Protocols for training and education of patient/caregiver
- Special precautions during nebulization of patients or suspects of the COVID-19 or or other contagious infections

Topics for Structure Training Module for the Doctors[19] *include: -*

- *Details of various inhalation devices and their proper use*
- Aim and principle of nebulization with emphasis on its domiciliary use
- Various types of nebulizers, their parts, comparison, and functionalities
- Purpose of domiciliary nebulization and selection of equipment

- Indications of home nebulization, whom to give, how long to give and explore possibility for switchover to handheld devices as and when possible
- All about drugs, dosages, their preparation, and compatibility on mixing of drugs
- Nebulization technique (method of inhalation, adequate gas flow rate, fill volume, duration, use of filter)
- Duration of nebulization, what is the endpoint, and the residual volume
- Difficulties and problems faced during the use of domiciliary nebulization therapy
- Driving gas in the nebulizers and when and where to use oxygen driven nebuliser and precautions to be taken with reference to cases of COPD
- Side effects of the therapy, both local and systemic; warning sign and remedies
- Special care in patients with comorbidities and elderly
- Instructions during travel
- Regular cleaning and disinfection of the equipment.
- Servicing and long-term maintenance of the equipment
- All about interfaces and how to choose suitable interface for patients
- Emergency action plan for acute exacerbation
- Regular monitoring and assessment of the patient during the follow up
- Nebulization for palliative respiratory care of patients
- Protocols for training and education of patient/caregiver/and HCWs
- Health related issues of the caregiver must also be addressed properly
- Special precautions during nebulization of patients or suspects of the COVID-19 or or other contagious infections

Evidence statement:

- There should be individual training modules for doctors, health care workers, patients and caregivers. Those modules should include detailing on the parts of the nebulizer and the nebulization technique; the medication; care of the equipment including cleaning, disinfection and maintenance; warning signs, etc.
- Sample modules for various categories have been provided. These modules help provide a uniform education pattern for every category and these can be modified also according to the local requirements.

Recommendations:

- The topics for the education of the patients, caregivers and health care workers should include the details of equipment, drugs and dosages, technique, cleaning, disinfection, maintenance, and emergency action plan for acute exacerbation etc. [UPP].
- The topics for the education of the doctors should include inhalation devices, types of nebulizers, indications of home nebulization; drugs, dosages, and side effects; technique of use, duration and difficulties; cleaning, disinfection and maintenance; assessment and monitoring; emergency action plan; patients/caregivers education; and follow up etc. [UPP].
- Modules for various categories have been provided which are recommended to be modified according to the local conditions and requirements. [UPP]

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Section - VI (Group - F): Nebulization therapy in COVID-19 pandemic and in patients of other contagious viral respiratory infections.

Abbreviations

ANZICS - Australian and New Zealand Intensive Care Society
ARDS - Acute Respiratory distress syndrome
ASV - Adaptive Servo Ventilation
Auto-PAP - Automatic positive airway pressure
BiPAP/BPAP - Bi-level positive airway pressure
BPM - Breaths per minute
CDC - Centre for Disease Control and Prevention
cm - Centimetre
CO2 (CO_2) - Carbon dioxide
COPD - Chronic obstructive pulmonary disease
COVID-19 - Coronavirus disease – 2019
CPAP - Continuous positive airway pressure
ETT - Endotracheal tube
FEV_1 (FEV1) - Forced expiratory volume in one second
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
H1N1 - Influenza A - H1N1
h - Hour
HCP - Health Care provider
HFNC/HFNO - High Flow Nasal Cannula/High Flow Nasal Oxygen
HME - Heat-and-moisture exchanger
ICU - Intensive care unit
L/min - Litres per minute
MDI - Metered dose inhaler
MERS - Middle East Respiratory Syndrome
mg - Milligram(s)
mg/mL - Milligram(s) per millilitre
mL (ml) - Millilitre(s)
MMAD - Mass median aerodynamic diameter
MV - Mechanical ventilation
μ (μm) - Micron (Micrometre)
N-95 - A particulate filtering facepiece respirator that meets the United States National Institute for Occupational Safety and Health (NIOSH) N95 classification of air filtration. i.e. filters at least 95% of airborne particles
NICE - National Institute for Health and Care Excellence
NIV - Non-invasive ventilation
OAD - Obstructive airway diseases
O_2 - Oxygen
PPE - Personal protective equipment
SARS - Severe Acute Respiratory Syndrome
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus – 2
$TCID_{50}$ - Fifty-percent Tissue Culture Infective Dose The tissue culture infectious dose defined as that dilution of virus required to infect 50% of the cell monolayers
UK - United Kingdom
UPP - Universal practice point
VMN - Vibrating mesh nebulizer
WHO – World Health Organization

Introduction

Nebulization therapy remains the cornerstone in the management of obstructive airway diseases (OADs) and is often used for the delivery of bronchodilators, corticosteroids as well as other medications for the management of these cases,

particularly in children and in the elderly population. Nebulization therapy delivers a therapeutic dosage of a drug through inhalation of drug-aerosol, generated with a drug solution or suspension, by a nebulizer via the mouth, and/or nose into airways and lungs. It has a relatively lower requirement for the patient's coordination and is often used at home and during emergent situations with concomitant oxygen therapy as a convenient choice for pre-hospital and in-hospital emergency care. In the present time, nebulization is gaining more importance and is increasingly being used as one of the inhalation therapy, particularly in children and in the elderly population.

The current global pandemic of coronavirus disease 2019 (COVID-19) caused by a novel Coronavirus named, SARS-Coronavirus-2 (SARS-CoV-2), has been responsible for many cases and deaths across the world. The virus is transmitted from a patient to others in the vicinity through aerosols generated from the infected respiratory mucosa and released into the atmosphere through breathing, talking, coughing, and sneezing. Transmission of SARS-CoV-2 to health-care personnel (HCP) and others through aerosol-generating procedures (AGPs), including frequently used nebulization therapy, is also a point of great concern. During the early phase of this period, several patients of OAD, undergoing nebulization therapy, in the event of being infected with SARS-CoV-2 or even on its suspicion, were shifted to other inhalation devices, mainly the metered-dose inhalers (MDI), out of fear and apprehension of transmission of infection to others. This often led to an improper use of these new changed devices due to factors including physical and mental fitness of the patient; improper training and instructions; resulting in poor drug delivery and thereby inadequate control of their disease.

Presently, there does not exist adequate evidence either to support or oppose the risk of transmissibility of SARS-CoV-2 during nebulization in COVID-19 patients with or without OAD. These doubts also sometimes arise in patients with OAD undergoing nebulization therapy who are either suspects or in whom the status of COVID-19 is uncertain. Similar problems are also foreseen in other contagious respiratory viral infections which are likely to emerge in future or which have existed in the past including influenza, severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and infections caused by other viruses.

Not much information is yet available on SARS-CoV-2 on issues of transmission of infection, however, information related to SARS-CoV and MERS-CoV which are closely related to SARS-CoV-2, has also been useful to provide some guidance in sorting out these controversies. According to the available current information, the risk involved with nebulization in the COVID-19 cases in transmitting the infection to the HCP and bystander hosts is low. There is not sufficient evidence to classify nebulizer therapy as an AGP, for the transmission of SARS-CoV-2, and requires more research. However, it is also equally important to undertake preventive measures to safeguard against even this small risk of transmission. As the current COVID-19 pandemic prolongs, more useful data will be generated, which may provide better information on this issue in the future.

Here, we are making certain observations and recommendations, in this chapter, based on all the current information and evidence available, related to these issues, which may be useful in the nebulization therapy during this COVID-19 pandemic and during similar situations arising in the future, with other viruses. This will also be useful in providing some guidance in nebulization during epidemics and pandemics with other contagious existing respiratory viral infections and some new ones that may emerge in the future and in such isolated cases too. This chapter provides most of the information available in the present time on the risk of transmission of infection from nebulization in these cases, precautions to be taken to minimize this risk while nebulizing such cases, and other related issues in the form of questions:

Q1. What are the important contagious viral diseases of the respiratory tract; which epidemics and pandemics have occurred during the last decades; and what are the emerging high-risk viruses?

In the recent past, there has been an increase in the rate of new emerging respiratory viral infections which is happening because of several global factors. These include the growing human population, increasing urbanization, changing interactions between men and animals, universal climate change, growing international travel and increasing global trade. Changing scenario of emergence of highly pathogenic strains of influenza viruses has cropped up as a potential danger for the viral pandemics, although in recent years, novel zoonotic coronavirus outbreaks have come up as new serious threats responsible for great morbidity and mortality in the human populatio.[1]

Various contagious infections of viral origin, affecting human population, include those caused by influenza virus, coronavirus, adenovirus, human metapneumovirus, respiratory syncytial virus, and rhinovirus.[2] Of all these viruses, influenza has been the cause of most pandemics, during the twentieth century. Unlike seasonal influenza, pandemic influenza viruses are the new virus strains that have not circulated in humans before, and to which humans have little or no immunity. They have the potential to cause significant morbidity and mortality and the ability of human-to-human transmission, thus they could easily spread globally. Four pandemics (Spanish flu in 1918, Asian flu in 1957, Hong Kong flu in 1968 and pandemic influenza A(H1N1) in 2009 have occurred since the early 20th century. Although the most recent of these due to influenza A (H1N1) pdm09 was not as severe as the Spanish flu but the rate of patients requiring intensive care unit (ICU) admission was much higher than that due to seasonal influenza.[3]

The influenza pandemic of 1918 has been estimated to have affected about 500 million people globally, causing 50-100 million deaths.[4,5] This pandemic virus shared properties with swine H1N1 virus and in all probability had originated from an avian influenza virus, undergoing several mutations and gaining the ability to access humans. The ability of viruses to jump

the species barrier and cause severe human infections is not limited to influenza virus but is seen with others too. These recent emergent respiratory viruses include: H9N2 (Hongkong 1999); SARS-CoV (Hongkong 2003); H7N7 (The Netherlands 2004); H3N2 (Canada 2005); H1N1 (Mexico 2009); MERS-CoV (Saudi Arabia 2012); H7N9 (China 2013); and SARS-CoV-2 (China 2019).[1]

Besides the spread of these viruses through the aerosols generated by coughing and sneezing in the host case, there is also a great threat of these infections spreading through the aerosol generating procedures (AGPs) performed over infected patients, necessitating adequate steps for their protection. We also need to consider those emerging viruses that could be a threat to cause nosocomial transmission to HCP, through these AGPs and we need to study and understand the mechanisms behind these procedures that have the potential to spread the infection. These viruses must have the capability to opportunistically infect others via the aerosol route and these must also be present in the cells and tissues where the procedure is being performed.

There are also infections with high risk, defined as both, a high likelihood of infection if an aerosol is inhaled or contacts a mucous membrane; and a high case-fatality rate for the viral disease; and where prophylactic or therapeutic options are limited. These mostly include biosafety level 3 and 4 viruses; excluding those causing measles, mumps, and rubella; having the potential to infect through the aerosol route and spread via the AGPs, but having a common vaccine protecting the HCWs. It also includes other viruses such as Norwalk virus, enterovirus, or human RSV, which may either lead to self-limiting diseases or are primarily pathogenic in paediatric, pregnant, or immunocompromised patients. Infection control measures must be followed against all these viruses, to protect other patients, HCP, and hospital visitors who are at risk of nosocomial virus transmission.[6]

Much is not known about the viruses that pose a high risk of infection to the HCP through performing AGPs, since these are often new emerging zoonotic viruses, which usually do not infect humans in contrast to those viruses that have adapted to the humans. These novel, high-risk viruses for HCWs performing AGPs have been listed in the Table 1.

Table 1 – Emerging viruses that may pose a high risk to HCP when performing AGPs.[8]

Arenaviridae
i. Junin virus
ii. Lassa virus
iii. Machupo virus
Hantaviridae, Nairoviridae, Phenuiviridae
i. CCHF virus
ii. Hantaviruses
iii. Rift valley fever virus
Coronaviridae
i. MERS-CoV
ii. SARS-CoV
iii.SARS-CoV-2
Filoviridae
i. Ebolaviruses
ii. Marburg virus
Orthomyxoviridae
i. Influenza A virus (H5N1, H7N9, pandemic H1N1)
Paramyxoviridae
i. Hendra virus
ii. Nipah virus

Many of these are also on the World Health Organization's (WHO) list of priority pathogens for research and development preparedness.[7] All of these viruses are emerging or re-emerging zoonotic RNA viruses which initially spill over from animal hosts into humans and then can undergo subsequent human-to-human and nosocomial transmission to cause epidemics. Many of these viruses are highly infectious and virulent too. but their transmissibility is low among humans; and these have evolved as true human respiratory viruses. Of these high-risk viruses, most belong to the families of coronaviruses, orthomyxoviruses, and paramyxoviruses. Many of these are becoming endemic in the human population (Table 1)[8]:

Out of all these emerging viruses, the family of coronaviridae and Orthomyxoviridae are the more common ones.The family Arenaviridae, contains multiple viruses that have the potential for nosocomial transmission (Lassa virus and Machupo virus) through AGPs but there is no evidence for human-to-human airborne transmission. Among the group of *Hantaviridae, Nairoviridae, Phenuiviridae*, Crimean–Congo haemorrhagic fever (CCHF) orthonairovirus, Andes hantavirus, and Rift valley fever virus are also associated with nosocomial transmission through AGPs and it is only the Andes hantavirus that is known to be transmitted from person to person, typically like respiratory viruses.

Filoviruses consisting of Ebola virus and Marburg virus, again are unlikely to have airborne transmission, yet it is possible that AGPs could create infectious EBOV-laden aerosols that could lead to nosocomial transmission. Again, the recently

emerged Nipah and Hendra viruses from the family Paramyxoviridae pose a high risk of infection through AGPs in the HCWs.

The Orthomyxoviridae family contains both human and zoonotic viruses and among these the influenza viruses are very well-known. Avian and swine influenza A viruses including H5N1 and H7N9 are some of the known subtypes that can be transmitted through aerosols to humans and also there have been few instances of nosocomial infections through the AGPs to the HCWs. However, the pandemic H1N1 and other influenza A virus subtypes are also known to have multiple such events.[8]

The family of Coronaviridae, are a group of RNA viruses that are known to transmit routinely between humans through the aerosol route. In humans, these viruses cause respiratory tract infections that can range from mild to lethal diseases. Mild illnesses include common cold, while more lethal varieties can cause life threatening respiratory infections.Three major corona virus epidemics have been reported which include SARS in 2003,[9] MERS in 2012,[10] and the current COVID 19 pandemic, caused by SARS CoV-2, reported in December 2019[11] It has been the SARS-CoV-2 which has resulted into lot of morbidity and mortality.

In 2002, from the southern area of China, a novel coronavirus (SARS-CoV) was reported causing severe viral pneumonia, later identified as severe acute respiratory syndrome (SARS).[12,13] The intermediate host of this virus was initially thought to be the masked palm civet bat, but ultimately it was found out to be the Chinese horseshoe bat[14] An infected physician from China travelled to Hong Kong in February 2003 spreading the infection and ultimately creating a global threat due to this virus,[12] Thereafter, it spread over the world rapidly with 8,273 cases leading to 774 deaths in more than 30 countries during one year period before its spread could be contained.[15,16]

In June 2012, nearly 10 years later, in Saudi Arabia, the first case of a new coronavirus, Middle East respiratory syndrome virus (MERS-CoV) emerged, leading to severe viral pneumonia, and it spread over to 26 countries leading to 2,468 confirmed cases and 851 deaths by Dec 2019.[17] Most of these cases (>85%) had a history of residence or travel to the Middle East countries (Saudi Arabia, United Arab Emirates, Qatar, Jordan, Oman, and Kuwait). Travel-related cases were also identified in other countries (Tunisia, the United Kingdom, France, Germany, and Italy). The intermediate host of this virus has been dromedary camels and bats as another possibility for transmission to humans.[18] However, it was also found out that MERS-CoV does not pass easily from person to person. (34.5%)

And now again after an interval of about seven years, an outbreak of novel SARS-CoV-2 was reported from the Wuhan district of China in December 2019, responsible for the current COVID-19 pandemic. It has already spread almost all over the world and is proving to be the deadliest of these diseases caused by coronaviruses in the past two decades, with nearly 525 million cases and more than 6 million deaths, reported at the time of writing,[5] and the numbers are continuously soaring.[19,20] SARS-CoV-2 has a 70% genetic similarity to SARS-CoV and it also resembles other bat coronaviruses. SARS-CoV-2 is capable of man-to-man transmission and hence has the potential for rapid spread among communities. The transmission of infection mainly occurs through respiratory droplets (large) but droplet nuclei (small) also contribute to it. A number of the AGPs also have a great role to play in causing nosocomial infection.

It is important to identify the contagious viral infections in patients undergoing treatment and to take adequate steps, to prevent spread of infection through, either human to human, or through the nosocomial routes, including infection through AGPs.

Evidence statement:

- Contagious viral infections of the respiratory tract are many and these are on rise and are also more frequently encountered now. These have led to several epidemics and pandemics in the past with considerable morbidity and mortality.
- Global factors such as growth in human population, urbanization, interactions between human and animals, climate change, and increases in travel and trade have been responsible for emerging respiratory viral infections during the recent past
- Various contagious respiratory viral infections affecting humans include Influenza viruses, Corona viruses, Adenoviruses, Human metapneumoviruses, Respiratory Syncytial viruses, and Rhinoviruses, with influenza virus being the commonest.
- Four pandemics that occurred earlier included Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968) and pandemic influenza A(H1N1)pdm09 in 2009
- The recent emergent respiratory viruses jumping the species barrier and causing human infections include H9N2 (Hongkong 1999); SARS-CoV (Hongkong 2003); H7N7 (The Netherlands 2004); H3N2 (Canada 2005); H1N1 (Mexico 2009); MERS-CoV (Saudi Arabia 2012); H7N9 (China 2013); and SARS-CoV-2 (China 2019)
- The current pandemic of COVID-19 caused by SARS-CoV-2 has been responsible for an extremely high morbidity and mortality globally.
- SARS-CoV-2 and several other existing and emerging viruses carry a risk of infection to HCP through man-to-man transmission and/or through aerosol generating procedures (AGPs) performed over infected patients at home, medical facilities, or hospital.

- These emerging or re-emerging zoonotic RNA viruses, many on WHO priority list, that pose a high risk of infection to HCPs during AGPs performed include mostly - Arenaviridae; Hantaviridae, Nairoviridae, Phenuiviridae; Coronaviridae; Filoviridae; Orthomyxoviridae, and Paramyxoviridae
- Infection control measures must be properly followed against these viruses to protect the contacts (patients, HCP, and hospital visitors) who are at an increased risk of nosocomial infections.

Recommendations:

- Patients suffering from contagious respiratory viral infections need to be identified to prevent transmission of the infection to HCP and other contacts by taking adequate preventive steps. A large variety of viruses can be responsible for these contagious infections [UPP]
- The spread of infection from these contagious cases occurs, both, from man-to-man transmission and through AGPs performed on these patients, which require adequate control measures to prevent transmission of infection. [3A]
- Viruses that pose high-risk mostly belong to families of coronaviruses, orthomyxoviruses, and paramyxoviruses, however others - Arenaviridae; Hantaviridae, Nairoviridae, Phenuiviridae; Filoviridae also belong to same category. Not all these have human-to-human airborne transmission, but some only have the potential for nosocomial transmission due to AGPs [UPP]
- There must be preparedness to deal with the epidemics and pandemics occurring in the future with the current or new emerging or re-emerging respiratory viruses to prevent morbidity and mortality in the population. [UPP]
- A regular surveillance for new emerging viral infection must be done allowing adequate and timely intervention to prevent their spread and spill over from animal hosts to humans and later human-to-human transmission. [UPP]

Q2. What are the physical characteristics; aerodynamic and dispersion properties; and fate of the aerosol generated by an infected patient during breathing, talking, coughing, sneezing and during their nebulization with reference to the transmission of infective organisms?

The deposition of the infected inhaled particles in the respiratory tract in a person exposed to infection is governed by the aerodynamic characteristics of the aerosol generated from the source case. Various deposition mechanisms can come into play, including inertial impaction, gravitational settling, Brownian motion, turbulent deposition, interception, and electrostatic attraction to govern their fate.[21] The larger particles (>8μm) are deposited from the nasal passage to the bronchioles by their gravitational force and due to inertial impaction in the upper airways. Effective filtering in the nose usually prevents large particles >5μm to penetrate further. Once the virus in these large particles are deposited in the nasopharyngeal region it can pass through the mucous membranes to replicate and continue spreading to the lungs.[22] The smallest particles (<1−3μm) can diffuse directly deep into the lung tissue, where they get deposited in the alveoli by sedimentation, diffusion, and electrostatic attraction. Particles in the 2.5-5μm range are deposited in the trachea, while fine (≤2.5μm) and ultrafine particles (≤0.1μm), due to their small size, reach deep into the lungs, to be deposited in the alveolar ducts and sacs.[23]

The transmission of infection from a case having contagious viral disease has always been debated. The infection usually occurs through the aerosol, which is generated when an infected person coughs, sneezes, talks, or even breathes. Basically, the aerosols are liquid or solid particles suspended in air and are produced when air passes over a layer of fluid.[824-26] The amount of aerosol generated while sneezing is maximum (Few hundred thousand to a few million), followed by coughing (Few hundred to many thousand) and is minimal while talking (Few dozen to few hundred or a few thousand).[27] The total amount of aerosols produced also is variable between the individuals, with some people creating very few, while others acting as "super producers". These super-spreaders of infection have been identified amongst SARS and COVID-19 patients, and it appears that this small population may be responsible for disseminating the majority of exhaled aerosol.[24]

The larger particles in the aerosol, called droplets (>5μm), rapidly drop to the ground by force of gravity, mostly within 3 to 6 feet of the source person, before they can evaporate. The transmission of the infection through these large droplets is usually called "droplet/contact spread". The disease transmission through this mode occurs when one touches a surface contaminated by these droplets and then touches his/her nose, mouth, and eyes; or by getting into the spray zone when the patient is coughing.[28]

The smaller droplets or particles (≤5μm), often called as aerosol, rapidly evaporate in the air, leaving behind droplet nuclei that are small and light enough to remain suspended in the air for hours, depending on environmental factors like temperature and humidity. These are free to float exceptionally long distances, causing what is often referred as "airborne" transmission. According to most of the sources, speaking, coughing, and sneezing generates droplets that are small enough to remain airborne and almost 80-90% of these particles generated are smaller than 1 μm in size, but their precise size is not known.[24,28,29,30,31]

Transmission of the disease from these fine aerosols depends heavily on their numbers produced, the concentration of the infectious agent in it, the virulence of the microbe, environmental factors (survivability of the virus, whether in the air or on a surface, until it enters a host), and the health and immunity of the host. In spite of the fact that though these fine aerosols are commonly produced, it is also evident that the vast majority of disease transmission occurs among people who are in very close contact and therefore are likely to be exposed to the largest of the droplets.[25]

It is important to know the time that a droplet remains suspended in the air which will influence the distance travelled by it and thus the exposure risk to the HCP and others. Usually, a 1000 μm droplet will be able to travel 1 meter in 0.3 seconds and then it will fall down. Similarly a 100 μm droplet will take 3 second for 1 meter, a 10 μm droplet will take 300 seconds, and a 1 μm droplet will take 30,000 seconds.[25] Chen[30] has suggested that various factors that influence the distribution of droplets and aerosols between 0.1 and 200 μm size include ventilation pattern and the initial velocity of the droplet when expelled out, rather than on the gravitational forces. Therefore the viability of aerosolized viruses in a droplet and their distribution is influenced by several factors, including temperature, relative humidity, ventilation pattern, ultraviolet radiation, gas composition of the air, initial velocity, and droplet nuclei size and composition.[27,30] Further, it has also been observed that most of these factors are dynamic since the droplet size changes as its liquid content evaporates and temperature also changes as one moves away from a febrile patient, making things more complex and difficult. Further, their are also other factors that have impact especially on the smaller size droplets and these include, Brownian motion, thermal gradients, electrical forces, and turbulent diffusion.[25,32]

Velocity at which the aerosol is expelled out is quite important in its dispersion into the environment which differs according to the the maneuver, like coughing and sneezing have the greatest initial particle velocities.[25] According to one of the studies, normal breathing have the lowest velocity at which the particles are expelled, approximately 1 m/sec, whereas while talking it is 5m/sec, coughing 10 m/sec, and highest is with sneezing 20-50 m/sec.[27] Thus, even though large particles are often assumed to land close to the patient, that assumption may often be incorrect.[33] With normal breathing, large droplets mostly fall to the ground within a 2-meter radius, but they can evaporate also while these are airborne, and become small droplets.[29] Coughing and sneezing can propel these large droplets much further – at least 6 meters.[33] However, there are no definite estimates that a droplet will stop before a certain distance, and the statements made about the distance travelled by a particular size droplet, it is meant that most droplets will fall but may be not all.

Thus, the widely accepted infection control concept does not hold true that as long as one is 2 meters away from the patient, one is safe from infectious droplets. This is not quite evidence based, and there is enough data to disprove it and this distance can no longer be taken as a definitive cut off point. This concept that all large droplets will be falling down within 2 meters was initially proposed by Wells, based on overly simplistic calculations and limited data, with assumptions, that have since been questioned.[27,28]

As such, the patients on their own are producing large quantities of aerosols, the AGPs contribute further to it and some of the procedures also require close presence of HCP which further enhances the possibility of transmitting the infection. Even if some of these procedures do not produce more of the aerosols, their ability to further spread the aerosols produced by the patients, is also a matter of big concern.[34,35] Essentially any air passing through the respiratory tract will create droplets, but the clinical significance will depend on the number of droplets produced, their size, the concentration of infectious agents, the frequency with which the activity is performed, and the personal protective equipment (PPE) used by staff.[25]

Furthermore, it is also to be understood that not every droplet will carry a virus, and even if it does, it may not be enough for the disease transmission. Neeltje van Doremalen et. al.[36] have studied the stability of SARS-CoV-2 and SARS-CoV-1 in aerosols in the environment and on various kinds of surfaces. Aerosols (<5μm) containing these viruses (bio-aerosols) were generated using a nebulizer and were filled into a Goldberg drum to create an aerosolized environment. Both the virus remained viable in aerosols throughout the 3 hours duration of the experiment, but their infectious titre was drastically reduced from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ and $10^{4.3}$ to $10^{3.5}$ $TCID_{50}$ per millilitre of air for SARS-CoV-2 and SARS-CoV-1 respectively. While demonstrating stability on different surfaces, SARS-CoV-2 was found to be more stable on plastic (up to 72 Hrs.) and stainless steel (48 Hrs.) than on copper (4 Hrs.) and cardboard (24 Hrs.), though the virus titre were greatly reduced from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ and from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per millilitre of medium on plastic (after 24 Hrs.) and stainless steel (after 48 Hrs) respectively.

The number and size of the aerosol generated, large or small, all have critical relevance in the transmission of infection. Those infections which primarily spread through the large ones, called as respiratory droplets, wearing a simple medical mask, using a face shield, or keeping 6 feet distance from other individuals, is enough to prevent transmission. If, however, it is carried by small size aerosols, called droplet nuclei, it can remain suspended in the air for prolonged periods; and medical masks would be inadequate, and would require N-95 respirators, and moreover, 6 feet of separation would not provide sufficient protection.[37]

Recently investigators have demonstrated in SARS-CoV-2 infections that speaking and coughing produce an aerosol, containing a mixture of particles of different sizes, large and small both, that travel for up to 27 feet, and remain suspended in the air and remain viable for hours. Some studies have shown that SARS-CoV-2 virus as well as their RNA are recoverable from the air samples taken in hospitals, and with poor ventilation these remain airborne for prolonged periods.[33] Many of these features have previously been demonstrated for influenza and other common respiratory viruses. These data provide a useful theoretical framework for possible aerosol-based transmission for SARS-CoV-2 also, but what is less clear, is the extent to which these characteristics lead to infections.[37] The World Health Organization's (WHOs) viewpoint is that detection of RNA in environmental samples based on PCR-assays is not always indicative of viable viruses that can be transmitted to others. The fact that speaking and coughing can generate aerosols or simply the recovery of viral RNA from the environment does not confirm aerosol-based transmission; but there are several other factors such as the route of entry,

duration of exposure, the size of inoculum, and host defences which also can influence it.[37,38] WHO in a recent scientific brief on some studies conducted in health care settings where symptomatic COVID-19 patients were cared for, but where AGPs were not performed, reported the presence of SARS-CoV-2 RNA in air samples. However, they also observed that no studies have found viable virus in air samples and within samples where SARS-CoV-2 RNA was found, the quantity of RNA detected was in extremely low numbers in large volumes of air. Only one study, that found SARS-CoV-2 RNA in air samples, reported inability to identify viable viruses. The detection of RNA using reverse transcription polymerase chain reaction (RT-PCR)-based assays is not necessarily indicative of replication- and infection-competent virus (viable) that could be transmissible and capable of causing infection.[33,39,40]

There always has been a controversy whether SARS-CoV-2 is spread by airborne route or not. Some organizations, including WHO, had stated very strongly that SARS-CoV-2 is not spread by the airborne route. However, others say the opposite, including the CDC guidance for coronaviruses, which has always been to treat them as airborne, although that too is based more on the precautionary principle than hard science.

Thus, though one can not be certain that transmission of SARS-CoV-2 is through airborne aerosols, in all probability this is likely to be an important mode of spread. The transmission of SARS and MERS, in the past, was also primarily considered to be through large droplets, but there was also evidences of spread occurring through the airborne route.[8,25,27,41] A retrospective analysis from Singapore also found poor ventilation in hospital wards as one of the five major factors responsible for the increased risk of transmission of SARS.[42] Recently, WHO has also changed their stand and have accepted the airborne route of transmission of SARS-CoV-2.

Presence of SARS-CoV-2 in the air, over six feet away from the patient, and its presence in the ventilation systems and even in the air in hallways outside patients' rooms; indicates the potential of aerosol in the airborne spread.[43,44] Guo found virus RNA in the air up to 4 meters from the patient[45] however, merely the presence of RNA is not the definitive evidence of presence of viable virus. On aerosolization of large volumes of SARS-CoV-2 the virus is likely viable for at least 3-5 hours or even beyond.[36,46] According to the National Academies of Sciences, Engineering, and Medicine, though the current research on SARS-CoV-2 is limited, the current data is consistent with aerosolization of viruses even from normal breathing."[47] Thus, it can in the present situation be safely concluded that airborne transmission of SARS-CoV-2 is possible.[28]

The aerosol generation can also occur during certain procedures in an infected person named as aerosol generating procedures (AGPs). The generation of aerosols depends mainly on the type of procedure, as some will produce more whereas others may produce less, however, whether the aerosol generated contains infective organisms or not, and how much, is also quite variable. In an updated scientific brief on COVID-19 transmission, WHO has said that the airborne spread of coronavirus occurs mainly with those medical procedures that generate exceedingly small droplets or aerosols. However, more research is urgently required to elucidate the importance of different transmission routes of the virus.[40]

Nebulizers, one of the AGP, generate aerosol particles mostly in the size range of 1-5 μm, that are capable of carrying the pathogens deep into the lungs. Some researchers speculate that the risk of droplet nuclei and aerosols related transmission may be more during nebulization since these generate large volumes of aerosols that have the potential to travel longer distances as against what is seen in the natural dispersion pattern.[48] Furthermore, the larger particles may stimulate the cough reflex in the patient and thus increase the risk of spreading the infection in an indirect manner to the HCP and the bystanders'.[49] However, whether this aerosol generated by nebulizer contains infecting organisms or not has been disputed since it is produced in the nebulization chamber. Hence it is not likely to transmit infection unless contaminated with respiratory secretions of the patient which may only occur on coughing or sneezing Thus, nebulization carries only a potential risk of transmitting infection to HCP and other bystanders. (Discussed in detail in Q. No. 3).

Evidence statement:

- Contagious viral infections from an infected patient spreads through aerosol generated from respiratory secretions. The aerosol deposition in the respiratory tract, in a host, is governed by their aerodynamic characteristics and by various deposition mechanisms.
- The particle size generated through talking, coughing, sneezing etc. and through Aerosol Generating Procedures (AGPs), in a patient, may be large (droplets) or small (droplet nuclei or aerosol), and the amount of aerosol generated is variable depending on the maneuver/procedure, and is also variable in between the patients with some acting as "super producers"
- The amount of aerosol generated while sneezing is maximum (Few hundred thousand to a few million), followed by coughing (Few hundred to many thousand) and is minimal while talking (Few dozen to few hundred or a few thousand)
- Larger particles (>5 μm) are filtered and deposited mostly in the nasopharynx where the virus enters into the mucous membrane of the host to replicate, spread, and produce disease. Particles in the range of 2.5 - 5 μm are deposited in the trachea, while fine (≤2.5 μm) and ultrafine particles (≤0.1 μm), reach deep into the lungs, to be deposited in the alveolar ducts and sacs.
- The large droplets (>5μm) drop down within 3 to 6 feet of origin, infecting people in this spray zone either through inhalation or through "droplet/contact spread" from touching the surfaces thus contaminated.
- The specified distance of 3-6 feet is not evidence based and has been found to be variable up to 27 feet. SARS-CoV-2, SARS-CoV-1 and MERS are transmitted mainly through droplets; however, airborne infection cannot be denied.

- The small droplets (≤5μm) evaporate rapidly to convert to droplet nuclei, light enough to remain suspended in the air for hours depending on several environmental factors and travel longer distances and are responsible for the 'airborne transmission' of disease.
- Transmission of infection through aerosols depends on their size and numbers; the concentration,viability and virulence of the virus in the aerosol; initial velocity; ventilation pattern; environmental factors; and the health and immunity of the host.
- Majority of transmission of infection occurs among people who are in close contact with the patient getting exposed to larger droplets, which drop down rapidly and at shorter distances.
- Though the virus may remain viable in the atmosphere and on different surfaces for a variable period, their concentration drops with the passage of time, thus the infectivity too. Merely the presence of viral RNA in air does not confirm infectivity.
- A medical mask and maintaining 6 feet distance is adequate to prevent infections with larger droplets whereas small size aerosols would require N 95 respirators and 6 feet distancing will not provide sufficient protection.
- Besides the aerosol generated by the patients in large quantities, AGPs further contribute to the risk of transmission of infection to the HCP, not only through further aerosol generation, but also often requiring close proximity to the patient
- Aerosols generated through AGPs have variable viral contents according to the organ and type of procedure. Nebulizers mostly generate a size range of 1-5um that has the potential to carry pathogens into the lungs, however, their role in transmission is not yet certain.

Recommendations:

- Aerodynamic properties of an aerosol and particulate deposition mechanisms govern the fate of aerosols inside the respiratory tract after their inhalation. It is recommended to study and understand the transmission dynamics of various contagious infections to help plan preventive strategies. (III B)
- Protection is recommended against droplets (large size) and droplet nuclei (small size) in cases with SARS-CoV-2, SARS-CoV-1, MERS, and other viral contagious infections. Both types of these aerosols are produced by talking, coughing, sneezing etc. and through AGPs performed on patients. (III A)
- SARS-CoV-2, SARS-CoV-1 and MERS are transmitted mainly through large droplets, however, airborne transmission can not be denied. Medical masks are recommended for protection against the large droplets and N-95 respirators for the smaller droplet nuclei. [III B]
- A minimum distance of 3 -6 feet, but preferably longer, is recommended to avoid infection through larger droplets from an index case and surfaces in this spray zone need to be disinfected properly to prevent infection through"droplet/contact spread". Distancing may not be useful in small size aerosols.(III A)
- The airborne transmission of infection through aerosols, that remain suspended in the air for hours and travel longer distances, is governed by several factors including their number, viability, and virulence of the virus; aerosol characteristics; environmental factors; ventilation pattern; and the health and immunity of the host. Preventive steps are recommended against this mode of transmission (IIIA)
- Factors that govern the dispersion and transmission of contagious infection must be optimized for better infection control (III B)
- Aerosols generated by nebulization, an AGP, are in the respirable range (1-5um) and can reach deep into the lungs but are unlikely to carry viruses and are considered relatively safe. However, it needs to be considered as a potential risk factor for transmission of infection (III A)
- Precautions are recommended to be taken even against this potential risk while nebulizing infectious patients. Further research and studies are needed to establish the status of nebulization in spreading the infection to HCWs and others. (III A)

Q3. What are various aerosol generating procedures and how much is the risk of transmission of SARS-CoV-2 and other contagious viral infections from nebulizer therapy?

Transmissibility of SARS-CoV-2 and other contagious viral infections is of great concern. SARS-CoV-2 and its RNA have been detected in upper and lower respiratory tract specimens and in the broncho–alveolar lavage fluid in the infected patients. It spreads from man-to-man, mainly through respiratory droplets, and to some extent the droplet nuclei, generated from the respiratory secretions in an infected person (bio-aerosols). These may transmit infection if they are able to land up on the mucosa of the nose, mouth, or in the eyes of people nearby, directly or indirectly. The aerosol may also be inhaled into the naso-pharynx and the lungs, leading to respiratory illnesses with complications like pneumonia and acute respiratory distress syndrome in some cases. Possibility of spread is more likely when people around are within about 6 feet distance from the patient.[50]

Aerosol-generating procedures are also now increasingly being recognized as important sources for nosocomial transmission of viral infections. During the recent epidemics of MERS-CoV and SARS-CoV, the high rate of nosocomial transmission seen has provided further support to the role of AGPs in transmission of contagious infections.[8] Moreover, studies from China have shown, 966 out of 5323 cases (18%) of SARS were from HCP, and during the early days of the outbreak, almost 90% of SARS patients were from frontline HCP.[42,51]

An AGP is a medical or surgical procedure that creates aerosols, in addition to those that the patient creates regularly from breathing, coughing, sneezing, and talking. The AGP's can produce both large and small droplets and these are generated either directly by the procedure itself or also indirectly by inducing the patient to cough or sneeze.[8]

These procedures (AGPs) may expose HCPs to various prevalent pathogens including current SARS-CoV-2, earlier SARS-CoV and MERS-CoV, and other infectious diseases including new emerging infections. Some of these procedures are more likely to generate higher concentrations of infectious respiratory aerosols than by coughing, sneezing, talking, or breathing. All these AGPs potentially expose HCPs and others to an increased risk of infection. There are also challenges in finding out whether reported transmissions during AGPs has been due to the procedure itself or due to other direct exposures while caring for the patient or getting exposed due to near proximity to them. Thus, the AGPs, besides leading to transmission of infection themselves by creating aerosols, also create situations which help make direct contact with the patient and their fomites for transmission to the HCP. This makes it difficult to find out the exact source of transmission, through AGP or directly from the patient, and it becomes difficult to distinguish the source. Fortunately, in absence of enough evidences nebulization has not been a part of the main list of AGP's responsible for transmission of infection.[50]

Various diagnostic and therapeutic AGP's are listed as under that may have the potential to generate uncontrolled aerosols from the respiratory secretions or by handling of the infected tissues (Table 2).[20,50]

Table 2 – Diagnostic and therapeutic AGP's.

- Non-invasive ventilation like Bilevel, C-PAP/Auto PAP/ASV/Home ventilation
- High flow oxygen
- Endotracheal intubation and extubation.
- Nebulization
- Bronchoscopy
- Sputum induction
- Airway suction
- Pulmonary function testing
- Chest physiotherapy
- Bag-mask ventilation prior to intubation (Manual ventilation)
- High frequency oscillatory ventilation
- Tracheostomy
- ENT procedures that trigger cough reflex
- Speech language therapy procedures that trigger cough reflex
- Surgery in the upper respiratory tract
- Cardio-pulmonary resuscitation
- Autopsy

It has not been possible to develop a comprehensive list of AGPs for the healthcare settings in absence of sufficient supporting data or the expert consensus. The challenge in determining, if reported transmissions of infection during a particular AGP is due to the procedure or other exposures, is another hurdle in preparing such a definitive list.

The AGPs can be grouped into two categories, including one where the procedures themselves create and disperse the aerosols mechanically, and the other where the procedure induces the patient to produce aerosols. Procedures like bronchoscopy or tracheal intubation irritate the airway mucosa making the patient to cough forcefully emitting virus-laden aerosols. Thus both these procedures indirectly increase the risk of transmission of infection.[52,53] Cardiopulmonary resuscitation can also by causing pressure on the chest of the patient, can induce a "cough-like force", that can lead to nosocomial transmission in SARS-CoV(54). Besides these the AGPs that themselves can create and disperse the aerosols, include procedures like mechanical ventilation and suctioning of the airways. It also includes manual resuscitators (bag-valve-mask); the non-invasive ventilation (NIV) like BiPAP (bilevel positive airway pressure) and CPAP (continuous positive airway pressure); HFNC (high flow nasal cannula); and HFOV (high-frequency oscillatory ventilation), all have been found associated with SARS-CoV nosocomial transmission. The exact mechanisms of production of bio-aerosols from the respiratory tract through these procedures is not well known; however, forceful to and fro movement of air could be responsible for it.[8,52,53,54]

The magnitude of the risk of transmission through AGPs is dependent on other factors also. The factors mentioned below can further aggravate this risk and those with these additional features are considered as "High-risk AGPs":[55]

- Longer duration of exposure
- Proximity of provider to aerosol
- Manipulation of high viral load tissue (nasopharynx/oropharynx have the highest viral levels).
- Aerosolization using energy devices (laser, cautery, drills, microdebriders, saws, & ultrasonic devices).

Further, there is limited data on some of these procedures, which creates an uncertainty about their generating infectious aerosols, and thus making it doubtful whether these at all pose any infection transmission risk. Some of such doubtful AGPs include the following:[50]

- Aerosol administration via a nebulizer
- High-flow oxygen delivery

There always has been a great apprehension on the risk of transmission of infection via aerosols generated during nebulizer treatment. A nebulizer generates aerosolized particles mostly in the range of 1-5 μm that have the potential to carry the microorganisms deep into the lungs. Moreover, a high volume of aerosols is generated during nebulization which can be propelled over long distances and become widespread. However, the aerosol generated is not the bio-aerosols that may have infection risk, but this may certainly contribute someway in the dispersion of the aerosol from the airways, hence nebulizers can very well be classified under the procedures that have doubtful transmission risk.

Delivery of nebulized medication therapy and high-flow oxygen, both can be labelled the aerosol generators, but with a lesser infective risk.[56] There has not been any direct evidence to show nebulization as the definitive cause for transmission of the infection but it is only supported by some such case reports that have tried to link transmission of infection to nebulizer use in the index patient.[57,58] One of the reports, however, has shown its doubts and points out that linking SARS transmission to nebulizer use is controversial. It is also difficult to distinguish the droplets, generated by the nebulizer itself, from those that are generated by the patient. It is only the latter that can be infectious, and that too only if these are present at all.

Simmonds et. al.[34] conducted a study to investigate droplet dispersion during oxygen therapy, NIV and nebulizer treatment (nebulized saline) in patients with coryzal symptoms and in patients with an infective exacerbation of chronic lung disease. During this study the droplets in ranges from 0.3 to more than 10 μm in mean diameter size were measured through two counters, one near the face and the other one metre away from the patient, at the level of the nose or mouth of an HCW. Nebulizer was the only intervention group, among these three procedures, that produced droplets in the size of aerosol range (<5 μm) which matched to the droplet size generated by the nebulizer used. These patients on nebulizer therapy, in both, coryzal groups and in the patients of chronic lung disease, could not detect droplets in the higher size range of 5 to 10μm and more than 10 μm, which were seen during NIV and oxygen therapy groups. This indicates that in the nebulizer group, most droplets produced are likely to be nebulized saline as opposed to patient droplet secretions, thus establishing safety of nebulizer from the risk of transmission of infection.[34]

The Public Health Agency of Canada[59] have tried to explain that aerosols with a larger diameter (10μm -100μm) can easily be deposited on *influenza receptors* on the host cells, found mainly in the mucosa of the nasopharyngeal. It is also important to understand that human influenza virus is transmitted only on the exposure to a sufficient infectious dose of a viable virus and their attachment to the receptors in a susceptible host. Thus, transmission of infection usually is possible with the *larger particles* when the susceptible host & infectious source are within proximity (<2 metres), since these large droplets drop down soon and do not travel longer distances. The contribution of smaller droplet nuclei to transmission of influenza is unknown. The nebulizers normally generate particle sizes in a range of <10 μm, majority are in respirable range (0.1 to 5 μm), hence their contribution in the transmission of influenza virus becomes an unlikely probability. Larger droplets, which are only few, some of these return to the reservoir feeding tube, while others settle on the walls of the baffle & only few may be released into the environment during expiration. These exhaled out aerosols are unlikely to contain infective virus in it since these are generated in the nebulization chamber, hence it can not transmit the infection. It is only when this aerosol is contaminated with the respiratory secretions of the patient, through coughing, sneezing etc during the procedure, that transmission can take place, but this risk is low or is unlikely. Therefore, larger particle sizes that usually can cause transmission are not produced by the nebulizer, if produced, these are unable to escape to the atmosphere, and mostly these remain within the system. Even though they can manage to leak out, they drop down soon (sedimented due to gravity) and are unable to travel even 1-2 meters because of their size. Further research is recommended to generate enough data in this field to have proper evaluation of the actual risk. Till we have enough data, proper preventive steps must be taken to safeguard against even this small potential risk. Thus, in the present, nebulizers can only be considered to have the potential to transmit the contagious viral infections to the HCP.[60]

The available data on the risk of infection due to nebulizer therapy during the pandemic of COVID-19 reveals extremely limited information since it has been a disease of recent origin and hence enough data could not be generated. However, information related to SARS, may also be useful about the current SARS-CoV-2, as both are quite similar and related infections. Two cohort studies reported some risks associated with nebulizer exposure in case of SARS, while another cohort study showed otherwise. The latter study by Wong et al. (2004) revealed that medical students performing bedside clinical assessment had an increased risk of contracting SARS infection even before nebulizer therapy was used.[41,52,61,62]

During 2002-2003 SARS-CoV outbreaks, a study on these patients undergoing treatment with a humidifier or a low volume nebulizer, in a healthcare setting, did not find evidence of SARS-CoV-1 -specific DNA products in any of the samples of air taken 30 cm. above the patient's head.[38] A review article by Tran et. al., including ten non-randomized studies on AGPs, utilizing evidence from the SARS outbreak, compared the risk of transmission of infection from AGP's in HCP compared to those HCWs caring for patients not undergoing AGPs. They could conclude that no significant evidence of transmission risk of infection directly related to nebulizers could be seen. They found that some procedures potentially capable of generating aerosols were associated with increased risk of SARS-CoV transmission, with the tracheal intubation being the most

consistent across multiple studies. There was also a strong association between multiple AGPs and transmission of SARS-CoV to HCP.[52]

The nebulization time is equally important in the transmission of infection, since the risk both direct and indirect, may be enhanced, if time duration is increased. Therefore, the vibrating mesh nebulizers (VMN) have a better safety profile because these generate aerosol at a much higher rate as compared to the jet nebulizers. The VMN has the shortest nebulization time and thus reduces the amount of aerosol lost in the atmosphere, minimizing the risk of transmission of infection. The VMN also produces more uniform and finer aerosol which makes it more useful and safer.[60]

The technologically advanced nebulizers, breath-enhanced and breath-actuated nebulizers also are more advantageous, since the drug released with these in the atmosphere is less during the exhalation as the aerosol generation occurs only during the inspiratory phase.[63] Breath-enhanced nebulizers use two, one-way valves, to prevent the loss of aerosol to the environment. The output rate is controlled by the patient's breathing. When the patient inhales, the inspiratory valve opens and gas vents through the nebulizer. Exhaled gas passes through an expiratory valve in the mouthpiece. Breath-actuated nebulizers are designed to increase aerosol drug delivery to patients by generating aerosol only during active inspiration. Consequently, loss of medication during the expiration phase is greatly reduced. Jet Nebulizer with collection bag can also be used where aerosol generated continuously fills into a reservoir and the patient inhales aerosol from the reservoir through a one-way inspiratory valve and exhalation through the exhalation port situated between the mouthpiece and the one-way inspiratory valve. Hence there is no spill over of aerosol during the expiratory phase.[64]

Using these advanced devices reduces the fugitive emission (aerosols that have been released from the device during patient expiration along with medical aerosols that are not inhaled by the patient but pass into the atmosphere) in the atmosphere reducing the chances of transmitting the infection. It is this fugitive emission which is considered as a potential source of infection. Up to 50% of the generated aerosol during therapy is fugitive aerosol which remains airborne in the indoor environment for several hours. The device, the interface, patient type, and flow rate, all have an effect on the quantity and characteristics of the fugitive emissions, while their dispersion and decay is influenced by the dimensions and layout of the room, air turbulence, airflow rates, and temperature. It is important to find out whether these nebulized aerosols present in the ambient air contain bioaerosols (generated by patients) or only medical aerosols (produced by aerosol devices), since COVID-19 can spread by bioaerosols only. Due to limited information and data in this field it is not certainly known whether bio-aerosol is generated during nebulization or not.[65]

Selection of an interface is equally as important as the device selection in the nebulization therapy. Using a face mask is to be avoided for nebulizer therapy in the management of COVID-19 patients especially while using a jet nebulizer since chances of fugitive emissions leaking out are more with it because of higher airflow rates. Jet nebulizers need to be used with a mouthpiece, preferably placing a a high-efficiency particulate air filter (HEPA), on the exhalation port of the mouthpiece. The other choice could be using a VMN with the mouthpiece along with a filter on the other end.[65]

So far no definitive links have been shown between nebulization therapy and increased risk of transmission of SARS-CoV-2 in the HCPs and it is quite difficult also to ascertain whether the so called possible risk is related to the use of nebulization or to an increased contact between the infected person and the HCP administering the treatment[50] The current United Kingdom guidance on infection prevention for COVID-19 has not yet listed nebulizers as a potential risk for transmission of infection since the aerosol generation occurs from the liquid drug in the nebulizer chamber and is not from the airways of the patient.[66]

The National Institute for Health and Care Excellence (NICE)[67] and the United Kingdom government guidance from the New and Emerging Respiratory Virus Threats Advisory Group[68] have recommended continued use of nebulizers since administration of medication through nebulization has not been considered as a significant infectious risk. The guidance seems rooted in the fact that the aerosol generated from nebulization treatment is not patient-derived but is produced from fluid in the nebulizer chamber, and hence, does not carry patient-derived viral particles. Moreover, even if the aerosol particles touch the contaminated mucus membrane of the airways it would get stuck there and cease to be airborne and will not be exhaled out as part of the aerosol.

The World Health Organization, in their recent document, has also emphasized on the insufficient evidence to classify nebulization therapy as an AGP that is associated with the transmission of COVID-19. They have also stressed on further research to be undertaken to resolve this issue.[69] The CDC also has stressed on absence of any definitive links between performing nebulizer treatments and increased transmission risk of SARS-CoV-2 infection. It is also difficult to ascertain whether the possible risk of transmission, if any, is causally related to the nebulizer therapy or is due to increased contact between the infected person and the HCP administering the treatment. However, it has also been emphasized for early detection and isolation of COVID-19 cases and regular and proper use of PPE by the HCP.[50]

Evidence statement:

- Transmission of infection from patients of SARS-CoV-2 or other contagious viral infections occurs through bio-aerosols produced by patients during breathing, talking, coughing, and sneezing; and also through aerosol generating procedures (AGPs) used on them.

- Enough supporting data is yet not available on the potential of nosocomial infections through these AGPs, used for various diagnostic or therapeutic purposes, and the risk of infection is also quite variable between them. Some of these procedures even produce higher concentrations of aerosols than the patient himself.
- The aerosol produced by these AGPs may be in the form of large droplets or small droplet nuclei generated by the procedure itself and also partly through induction of cough or sneeze in the patient.
- These AGPs, besides producing aerosols, also enhance the possibilities of HCW and others contracting infection by coming in close contact with the patient (through airborne route or their fomites) making it difficult to differentiate between the two.
- Various AGP's with the potential to generate aerosols from the respiratory secretions or handling of the infected tissues, in different ways, have been enlisted in the table-2, however, developing a comprehensive list is difficult in absence of supportive data and expert consensus.
- The AGPs can be grouped into two, one where procedures themselves create and disperse aerosols mechanically and in the other these procedures induce the patient to produce aerosols like in bronchoscopy or tracheal intubation.
- The exact mechanisms of generation of bio-aerosols in the respiratory tract remains unknown and various mechanisms have been proposed. There are several factors also associated with AGPs which increase the risk of transmission placing them in the category of "High-risk", and some as "Doubtful" AGPs.
- Limited data is available on nebulization, one of the AGPs, creating an uncertainty on its ability to generate infectious aerosols and thus also the risk of transmission of infection even though a high volume of aerosols (<10 μm) is generated.
- Nebulization, presently, is considered to carry a lesser infective risk since the aerosol is not patient-derived but is produced from fluid in the nebulizer chamber (medical aerosol), hence, does not carry virus, unless contaminated with respiratory secretions of the patient (bioaerosols generated during coughing or sneezing).
- In absence of proper evidence it has neither been possible to establish a link between nebulization therapy and transmission of infection to the contacts nor it has been proved to be a safe procedure. Further research is needed to establish this fact.
- Presently, it is recommended to continue use of nebulizers, however, isolation of such patients, and taking all possible infection control measures and preventive steps, is advised, whether at home or in a medical facility.
- Technologically advanced nebulizers such as VMN, breath-enhanced, breath-actuated and those with reservoirs are relatively safer, either due to a short nebulization time or by generating aerosol only during inspiration or aerosol getting collected in a reservoir. Placing a filter at the exhalation port makes it more safe.
- Mouthpiece as an interface is safer and use of facemask is not recommended.
- Presently, it is difficult to ascertain whether the possible risk of transmission due to nebulization is causally related to the use of a nebulizer or due to increased contact between the infected person and the HCP administering the treatment. The increased exposure time of HCP to the infected person also contributes to the risk, both through airborne route and transmission through fomites.

Recommendations:

- The infection from SARS-CoV-2 or other contagious viral infections are spread through bio-aerosols produced by patients and through aerosol generating procedures (AGPs) performed on them. Adequate preventive measures are recommended to be taken against them. (III A)
- Cautious use of various AGPs is recommended in these patients since these have a potential to transmit infection to health care personnel (HCP), however, the risk is variable in between different AGPs (III A)
- The AGPs besides producing aerosols on their own also sometimes cause induction of cough or sneeze producing bio-aerosol contributing to the transmission of infection. (III A)
- The AGPs also allow close contact with patient enhancing chances of infections through aerosols and fomites requiring adequate preventive measures (III A)
- The aerosol generated from nebulizer treatment carries a lower risk of infection since it is not patient-derived (bioaerosols) but is produced from fluid in the nebulizer chamber (medical aerosol), and hence, does not carry viral particles. (III A)
- Presently, it is recommended to continue use of nebulization, even though it is included as one of the AGPs, since no definite link has been found between use of nebulization and increased risk of transmission of infection. However, it is considered to carry a potential risk of transmission of infection. (III A)
- It is recommended to take proper preventive steps during nebulization as the possible risk of transmission due to nebulization may not only be causally related to the use of a nebulizer but also due to increased contact and contact time between the patient and the HCP administering the treatment through patient's generated aerosol and fomites (III A)
- All types of the nebulizers can be used; however, preference be given to technologically advanced nebulizers such as VMN, breath-enhanced, breath-actuated and nebulizers with reservoirs, which are considered relatively safer. It is also recommended to use an additional filter at the exhalation port (III B)
- Use of mouthpiece as an interface for aerosol therapy is recommended while nebulizing infected patients, especially with the use of jet nebulizers. Use of face mask is to be avoided due to increased risk of transmission of infection (III B)

Q4. How to minimize the potential risk of transmission of infection during nebulization in infected cases at hospital and home?

Aerosol generating procedures are known for the transmission of infection to HCP and some of these procedures are likely to generate higher concentrations of respiratory aerosols, even higher than coughing, sneezing, talking, or breathing of the patient. Such AGPs put HCPs at an increased risk for exposure to SARS-CoV-2 and other contagious infections. Enough data is yet not available to evaluate as to which particular procedures produce potentially infectious aerosols creating a risk of transmission of infection to the HCPs especially so in the patients of COVID-19.

There has been a great apprehension on the risk of infection transmission via aerosols generated during nebulizer treatments. Their use is further increased during the epidemics and pandemics caused by contagious respiratory viral infections. However, there has also been uncertainty about the infectiousness of some of these procedures including nebulization.[50] Presently, its use has neither been established as a risk factor nor has been declared safe for the transmission of SARS-CoV-2 and other contagious viral infections. Therefore, in the present time, nebulization, for not having a clarity on its status, WHO and CDC, both recommend its continued use as a procedure carrying a potential risk. However, early recognition, isolation of such patients, and taking all possible infection control measures and preventive steps by HCP during the procedure is recommended. Other organizations also advise for the continued use of nebulizers as it is not considered to represent a significant risk, though some recommend switching to MDIs in those who can use and tolerate it.[50,67,68,69,70,71]

While nebulizer treatment continues to be administered in hospitals and health care facilities, one has to be cautious and is required to adhere to strict measures and protocols to protect HCP from contracting these contagious respiratory viral infections. This includes stringent sanitization protocols and proper use of appropriate PPE kit. Centre for Disease Control, the Minnesota Department of Health, and WHO, have made some recommendations and have provided guidance to minimize risk of nosocomial infection to HCP while nebulizing a patient in a healthcare facility or at a hospital which are given in Table 3.[50,69,71]

Table 3 – Instructions to be followed for nebulization therapy.

- Selectively switch over to MDI with a dedicated spacer or other handheld devices if the patient can tolerate and effectively use it. However, proper training must be provided.
- HCPs should wear N-95 or higher version respirators along with an eye protection, face shield, gloves, and a long-sleeved gown during treatment. Facilities not having these provisions should not care for COVID-19 patients and instead transfer them to a better facility.
- The number of HCP present during the procedure should be limited to only those essential for patient care and procedure support. It is also advisable to limit the time of stay of HCP in the room without compromising patient care. Visitors should not be present during the procedure.
- Close the patient's room door when providing nebulizer treatment.
- Upon set-up of the nebulizer, the HCPs must maintain a safe distance (6 feet or greater from the patient), preferably stay outside the door after the set-up.
- AGPs should preferably be performed in airborne infection isolation rooms (AIIR), if available or in negative-pressure rooms with at least 12 air changes per hour and controlled direction of airflow. Alternatively, an adequately ventilated room should be used with natural ventilation with air flow of at least 160 L/s per patient
- HCP should use appropriate hand hygiene when helping patients remove nebulizers and oxygen masks.
- Clean and disinfect procedure room surfaces promptly with recommended disinfectants after nebulization is over.
- Patients do not need to be transferred to a higher level of care solely for the purpose of providing nebulizer treatment.
- Preferably, only disposable single use nebulization units be used and disposing of used ones properly after each use
- The COPD Foundation additionally recommends the use of a filter (equivalent to an N95 mask or HEPA filter) with nebulizers to filter the patient's exhaled air, and thus limit the risk of virus spread. [72]

Nebulizer use at home may be necessary for patients with asthma or COPD who may either be suspects or are established cases of COVID-19. This may be continued since no definite patient-related hazards have been shown to this therapy. However, it is important for the patient to follow routine infection control measures with some extra precautions like maintaining better hygiene of the nebulizer, avoiding standbyers while nebulizing, and preferring locations near open windows or at places of better air circulation to minimize the risk of infection to others. Some of the preferred locations could include outside on a porch or patio or in a garage, where there is no recirculation of the air into the home and where dependent surfaces,where droplets fall, can be easily cleaned. The number of persons during the procedure must be minimal in the nebulization room and social distancing guidelines must also be followed. If any HCP is present, they must use proper PPE. The nebulizer equipment should not be shared between family members and other patients.[50,71]

Use of telehealth should be considered and encouraged in such situations to evaluate coronavirus infected patients and suspects, staying at home, to minimize the utilization of healthcare facilities as much as possible. This could be a good option for evaluation and monitoring of these patients at home and smartphones can be used for this purpose.[65]

During the pandemic period, there are no specific restrictions for the nebulization in non-COVID-18 patients, who are suffering from asthma or COPD or any other ailment, whether at home or in the hospital, and they may continue taking their required nebulized drugs including inhaled corticosteroids, as recommended in the guidelines, or as prescribed by their physicians. However, there should be no indiscriminate use of nebulization and the assumption that nebulizers are superior drug delivery systems than other handheld devices, has well been dispelled by several studies. Since the nebulization has

the potential to transmit SARS-CoV-2 and other contagious infections to the HCPs and others present in the vicinity, its use must be restricted amongst only those who are unable to use other hand-held devices. On the contrary, it must also be always ensured that the individuals advised to use handheld devices, are physically and mentally fit to make use of them properly. It has been observed that many of these patients use these devices inaccurately (41%–69%) and make critical errors in at least 88% of patients,[73,74,75,76]

Evidence statement:

- Aerosol generating procedures in patients of SARS-CoV-2 or other contagious viral infections often pose a threat of transmission of infection to the HCPs and others.
- Various international organizations in the present time do not classify nebulization as one of the AGPs responsible for the transmission of SARS-CoV-2 or other contagious infections in absence of definitive evidence, however, they recommend adopting infection control measures and sanitization protocols during its use because of the potential risk of infection.
- It is also not ascertainable whether the possible risk of infection in these patients is causally related to nebulizer use or due to increased contact between the infected person and HCP.
- The preventive measures to be adopted during nebulization in infected patients include use of personal protective equipment (PPE), including N-95 or higher version respirator masks, double gloves, eye protection; and following other instructions mentioned in the box; both in health care settings and at home.
- Appropriate inhalation devices are to be selected on the merits in individual cases and indiscriminate use of nebulizers is to be discouraged and restricted only to those cases where other hand-held devices cannot be used.
- Nebulizer use at home in patients with contagious disease or their suspects should also follow routine infection control measures and undertaking extra precautions like selecting a place in areas of increased air circulation with no recirculation into home (porch, patio, or garage), where dependent surfaces are easily cleanable; presence of no or limited number of persons, HCP if present to use PPE kit, strictly following sterilization protocols.
- Telehealth should be considered as an option to monitor infected or suspect patients taking treatment at home.
- Nebulization in cases of asthma, COPD, or other ailments in non-infected patients, at home or hospital, during pandemics, need no specific restrictions and should continue with required drugs including inhaled corticosteroids

Recommendations:

- Though no definitive evidence is available for the spread of infection through nebulization in patients of SARS-CoV-2 or other contagious viral infections, it is recommended to be considered as a potential risk and precautions and preventive steps need to be taken accordingly. [III A]
- While administering nebulization to these patients in healthcare settings, strict adherence to measures that protect HCP (mentioned in the box) are recommended including stringent sanitization protocols and use of appropriate PPE. Nebulization should preferably be done in airborne infection isolation rooms (AIIR) or negative-pressure room [III A]
- It is recommended that home nebulization in COVID patients or their suspects may be continued with special attention to enhanced nebulizer hygiene; to be used at a place of increased air circulation without re-circulation into the home; where dependent surfaces are easily cleanable; and in absence of people or only bare minimum possible [III A]
- Indiscriminate use of nebulizers in general must be avoided and wherever feasible and appropriate other handheld inhalation devices be used. The technique of use of these devices must be proper. [UPP]
- Telehealth could be a good option to evaluate and monitor these patients at home and smartphones can be used for this purpose. (UPP)
- Nebulization in non-infected patients at home or hospital during pandemics is recommended to be continued in the usual manner with the prescribed drugs.(UPP)
- Sharing of nebulizers is not recommended. Hospitals and healthcare facilities should preferably use single use nebulization units. (UPP)

Q5. Are there any special precautions to be taken while nebulizing a patient with COVID-19 on mechanical ventilation, or non-invasive ventilation or on high flow nasal cannula (HFNC)?

Several patients with COVID-19 often may develop respiratory complications and some of the recently published studies show that almost two thirds of these patients may develop acute respiratory distress syndrome.[77] Many of such patients require intensive care and some even respiratory support after 9 to 10 days of their illness.[78] Nebulization may often be needed, in these critically ill patients, both with or without ventilatory support. For mechanically ventilated COVID-19 patients, both suspected or confirmed, use of nebulizer is recommended and approved, however, in these patients mechanical ventilation circuits must be kept intact to prevent the transmission of the virus to HCP. The in-line nebulizer should be preferred for nebulizing these patients since these are part of a closed ventilator circuit.[79]

It is not appropriate to deliver aerosolized medication via jet nebulizer or through pMDI, since these devices need a breakage in the ventilator circuit which is not desired. Recent Chinese guidelines have suggested the use of the mesh

nebulizer in critically ill patients, with COVID-19 receiving ventilator support,[80] since these have the benifit of staying in-line for up to 28 days. Their reservoir design can be used which does not require breaking up the ventilator circuit for aerosol drug delivery, avoiding possibility of contamination of the nebulization fluid since their medication reservoir is isolated from the breathing circuit.[65] Placement of these mesh or jet nebulizer has to be done proximal to the humidifier which further reduce retrograde contamination from the patient besides improving the efficiency of the treatment.[81,82]

The aerosol that is exhaled out in an intubated patient may remain suspended in the air and can be a serious risk of infection to the HCP as even low concentration exposure could be sufficient for the transmission of coronavirus. Ari et al. quantified the amount of aerosol collected at the exhaust outlet of a ventilator, using it with or without filters in the expiratory limb of the circuit. They found that drug deposited at the exhaust port without expiratory filters was more than 160 fold higher compaired to use with expiratory filters. They also found that second hand aerosol exposure is significantly reduced by placing a filter in the expiratory limb.[83] Hence, to prevent the possible transmission of bioaerosol to the HCP use of HEPA filters will be critical[65] In the other studies also similar findings were seen and a filter to the nebulizer was found to be 93% effective in capturing exhaled aerosol droplets.[83,84]

Sometimes chest physiotherapy or endotracheal suctioning are done simultaneously while nebulization is being done and the coughing thus induced may generate droplet nuclei containing corona or the other viruses that are capable of transmitting infection to the HCP in these mechanically ventilated patients. This practice, therefore, should not be adopted. In an intubated patient endotracheal suctioning should be preferred with in-line or closed system suction catheters since these can be utilized for up to 7 days without having to break the ventilator circuit and these catheters, of any design, can be used since no significant difference was found in aerosol drug delivery using different designs.[85]

Non-invasive ventilation (NIV) is now frequently recommended as a standard of care for the management of patients with acute or chronic respiratory failure. Such situations are very often encountered while managing patients with SARS-CoV-2, SARS-CoV, MERS or other viral infections. However, many times NIV may not prove to be efficacious in rescuing these cases of respiratory failure and there may be a likelihood of progression of some of these cases to intubation. In such situations HFNC is the preferred modality of treatment and only in situations where HFNC is not available, a short trial of NIV may be given. In such situations frequent patient reassessment must be done, and a decision to intubation should not be delayed if the patient is not improving or starts showing deterioration.[71]

A good number of patients undergoing NIV require aerosolized medications too. The routine practice in patients on NIV is that the mask is removed and nebulization therapy is administered to the patient. In some patients the nebulizer may be connected through the mask or to the ventilator circuit of the NIV and aerosol therapy is given. Thus, nebulization therapy can either be administered in these patients separately after discontinuing NIV for a short duration or it can be given simultaneously without interrupting the NIV support.[86] Combining NIV with the nebulized aerosol therapy, besides giving uninterrupted NIV support, has been found to be more efficacious than aerosol therapy alone in terms of spirometric variables in patients with OAD, particularly asthma.[87] Nebulizers that produce aerosols with a mass median aerodynamic diameter (MMAD) of less than 2 μm are found to be more efficient for a better lung deposition while using NIV simultaneously.[88] When using both together, the nebulizer should be placed at the mask or before the Y-piece of the double-limb circuit for the highest aerosol delivery. However, while using a single limb NIV circuit, various studies on aerosol therapy have shown the position of the nebulizer in between the exhalation port and the lung to be the best.[89,90]

Non-invasive ventilation has been included by the Minnesota Department of Health and CDC guidance as one of the AGPs.[50,71] According to one of the study, patients receiving NIV, exposure to exhaled air to the people around, occurs within a radius of 0.5 metre at the usual pressures and the higher NIV pressures result in still wider distribution of exhaled air. The NIV equipment is reusable and it gets infected when exposed to infectious material when used on an infected patient. If the equipment is not properly disinfected it becomes a source of nosocomial infection to a wide range of respiratory pathogens, hence, between uses, it must be properly cleaned and disinfecte[91,92] Indirect and low-certainty evidence from a study suggests, that NIV use increases the risk for transmission of COVID-19 to HCP but the risk could not be exactly quantified. Use of PPE is recommended to reduce this risk to some extent but it can not be abolished.[93] A consensus statement from Australia and New Zealand suggests that NIV should be assumed as an AGP until further data become available.[94] It has also been recommended that the interface must be of a good fitting which minimises the widespread dispersion of exhaled air and consequently lowering the risk of airborne transmission of infection from patient to others.[95]

The NIV equipment, after each use, must be disassembled, and its parts, especially the reusable mask and exhalation valves, must be properly disinfected. A washer, disinfector, and a dryer using heat are used for this purpose. The tubing can be autoclaved at 134°C for 3.5 minutes. Headgear and chin straps should be washed in a washing machine at 65°C for 10 min or at 71°C for 3 min. In most ventilators with inbuilt NIV function there is no airflow from the patient back into the ventilator, thus reducing the contamination risk of the ventilator to an extremely low level. However, it is advisable to use a bacterial filter system and a proper cleaning of the ventilator is done in between the uses.[92]

High-flow nasal cannula (HFNC) for oxygen delivery has also been included in the list of AGPs, however, limited data is available on it. During use of HFNC, simultaneous administration of nebulization therapy, have been enlisted as procedures which have an uncertain status on the infectiousness, among the patients with contagious viral infections. In the recent past, HFNC has emerged as an important option to reduce the rate of intubation and improve the clinical outcome in patients of COVID-19 having acute respiratory failure. Only few clinical studies on aerosol delivery during HFNC are available

and in view of the paucity of the data, no proper recommendation can be made either in favour or against aerosol delivery during HFNC. However, during the COVID-19 pandemic, CDC has shown doubts on the infectiousness of aerosols generated by HFNC. Although previous studies showed a low risk of airborne transmission with HFNC, when good interface fitting mask is used, however, the safety of using HFNC in patients with coronavirus, as well as the risk/benefit ratio for aerosol drug delivery through HFNC, has not been properly investigated.[50,65,96,97]

Various guidelines on respiratory support from several national bodies differ significantly on making a definite recommendation on the use of HFNC in the cases of COVID-19. The WHO recommends it only in selected patients having hypoxemic respiratory failure with facilities of proper monitoring of the case and also availability of staff experienced in endotracheal intubation, which may have to be done in the event of sudden deterioration in the condition or failure to improve after a short trial of about an hour. According to the guidelines of the Australian and New Zealand Intensive Care Society (ANZICS) on COVID-19, HFNC is a "recommended therapy" for hypoxia associated with COVID-19, but they also recommend use of proper PPE by the HCP. The Surviving Sepsis Campaign guidelines on COVID-19 have recommended HFNC over conventional oxygen therapy and NIV in all the non responders to conventional oxygen therapy in cases of acute hypoxemic respiratory failure. Based on the clinical experience on COVID-19 patients in China and the United States, preference has been given to HFNC over NIV in patients with hypoxemic respiratory failure.[71] Considering the limited facilities including the number of ventilators available in hospitals during epidemics and pandemics like COVID-19, use of HFNC could be a good option to prevent patients with asthma and COPD developing severe hypoxemic respiratory failure in such situations.[65,71,98,99,100]

It will be important to see whether HFNC translates into a significant infection risk on combining it with nebulization therapy. It is also important to see how this risk compares with use of other alternative respiratory supports and how much is the risk of infection to the HCP and how best they can be protected from infection during aerosolization. Use of adequate PPE is the most important precaution in the risk mitigation.[101] Fugitive emissions released during nebulization while managing patients with COVID-19 using HFNC is also a real concern since it does not have a closed circuit which leads to the risk of dispersion of aerosol. Though previous studies have shown a low risk of airborne transmission with HFNC when using a good fitting interface, howevr, its safety in patients with coronavirus infection as well as the risk/benefit ratio for aerosol drug delivery through HFNC, has not been well investigated. Previous studies have also shown that increasing the flow decreased the fugitive emissions and the particle size of aerosols during therapy. However, respiratory therapists while delivering this dual therapy, should always wear a proper PPE kit, which should include a N95 respirator, face shield, double gloves, and a fluid resistant gown or apron. Moreover, the aerosol therapy preferably be administered in a negative pressure room.[65]

Some patients who do not require high-flow oxygen to maintain adequate oxygenation may benefit from aerosol delivery while receiving low-flow oxygen via HFNC. Nebulized medication can safely be combined with low-flow oxygen through HFNC, in cases of COPD without interrupting the gas flow. The VMN is preferred over the jet nebulizer because these deliver larger doses to subjects in less time, however, there is no benefit of using the large spacer with low-flow delivery, since the large droplets preserved in the spacer can not pass through the small inner diameter of the HFNC to reach the patient.[102]

One of the studies has shown that bio-aerosol dispersion via HFNC shows a similar risk as seen with standard oxygen masks. In case aerosolized medication also needs to be delivered through HFNC in hypoxaemic COVID-19 patients, this risk of environmental transmission/contamination can be minimized by placing a surgical mask on the face of infected patients covering the nasal prongs. In routine, HFNC as a modality of treatment can be implemented as a regular practice in the hypoxaemic patients to give a trial to avoid need for intubation in some of them. Thus, clinicians need not have to restrain themselves from using HFNC in COVID-19 patients with respiratory failure.[103]

Delivering aerosolized medications through nebulization to COVID-19 patients, either on spontaneous breathing or on NIV or HFNC, have a great potential of transmitting infection to HCPs.[45] Use of good personal protection during aerosol administration must be an important prerequisite. (mentioned in Q. No. 4) It is also imperative during the pandemic to assume that all patients may be infected and be managed accordingly. (65).

(Note- See Question 10, Section III (Group C) also)

Evidence statement:

- Many of the patients with SARS-CoV-2, SARS-CoV, MERS or other viral infections, develop respiratory complications and some may need intensive care including mechanical ventilation, or NIV or HFNC and simultaneously may also require nebulized medications.
- For intubated patients requiring nebulizer treatment, in-line nebulizer as a part of the closed circuit, should be used to keep the circuit intact preventing transmission of infection to HCP. Use of nebulizers and pMDI is to be avoided which require breakage in the ventilator circuit. Among nebulizers, if required, a VMN is preferred over jet nebulizers, preferably with a medication reservoir, with their placement prior to the humidifier
- Use of HEPA filters in the expiratory limb of the ventilator circuit is useful in capturing the exhaled aerosol, reducing the second-hand exposure to HCPs, thus preventing the transmission of infection.

- Procedures such as chest physiotherapy and suctioning, simultaneously with nebulization in mechanically ventilated patients, is to be avoided which may enhance the risk of transmission of infection through cough induction. Endotracheal suctioning is preferably done by using in-line or closed system suction catheters, of any design.
- Non-invasive ventilation (NIV) is often required while managing SARS-CoV-2, SARS-CoV, MERS or other viral infections. Nebulization in patients on NIV, is done either after discontinuing NIV or by connecting the nebulizer to the mask or to the NIV circuit.
- Aerosol delivery is optimum when the nebulizer is positioned at the mask or just before the Y-piece of the double-limb NIV circuit whereas in single limb circuits it is between exhalation port and the lung.
- Combining NIV along with nebulized aerosol therapy has been shown to be more efficacious than aerosol therapy alone as seen on spirometry findings in patients with OAD, particularly asthma.
- NIV should be assumed as an AGP and proper preventive steps must be taken by the HCP to minimize risk of transmission of infection while using NIV and nebulization simultaneously.
- With the usual pressure settings in NIV, the dispersion of exhaled air occurs within 0.5 metre radius whereas higher pressures lead to a wider distribution of exhaled air. An interface with good fitting is recommended to minimise dispersion of aerosol in the exhaled air.
- The equipment, with the reusable masks and tubings, exhalation valve, headgear, and straps, must be properly disinfected after each use. Most ventilators used for NIV, are without an airflow back into it, minimizing the risk of contamination. However, a bacterial filter and superficial cleaning of the ventilator is advised.
- High flow nasal catheter (HFNC) is an important option for oxygen therapy to reduce the intubation rate and improve prognosis in patients of COVID-19 with hypoxemic respiratory failure and is preferred over NIV. However, it is also considered as one of the AGPs.
- HFNC has a higher risk of dispersion of aerosolized viruses since it does not have a closed circuit. There is paucity of evidence on the risk of infection through simultaneous use of nebulization and HFNC, though both individually, carry a potential risk.
- High-flow nasal prongs with a surgical mask on the patient's face might benefit hypoxemic COVID-19 patients without added risk of infection to the environment. Some patients not requiring high-flow oxygen may benefit from aerosol delivery while receiving low-flow oxygen via HFNC.
- Good personal protection and hygiene for HCPs is advised during nebulization in patients with SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections undergoing mechanical ventilation, NIV, or HFNC.

Recommendations:

- Use of in-line nebulizer as a part of the closed circuit is recommended for aerosol medication in mechanically ventilated patients with SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections. Use of HEPA filters in the expiratory limb of the ventilator circuit is also recommended. (III A)
- Use of nebulizers and pMDI during mechanical ventilation should be avoided since breakage in the ventilator circuit is not desired. Among regular nebulizers, VMN is to be preferred over jet nebulizers. (III A)
- Endotracheal suctioning is recommended by using in-line or closed system suction catheters, of any design, which do not require to break the ventilator circuit for upto 7 days. (III A)
- Simultaneous chest physiotherapy and suctioning is not recommended while nebulizing an intubated patient with contagious infection since it may induce cough. (III A)
- Nebulization in infected patients with hypoxemic failure, undergoing NIV, an AGP, is done by disconnecting NIV or by connecting the nebulizer to its circuit. The results are better with a combination of the two, however, the interface must be of good fitting to avoid dispersion of aerosol which is more with higher pressure settings of NIV. (III A)
- Positioning of the nebulizer in the NIV circuit, for optimal therapy, is done at the mask or before the Y piece in the double limb circuit. In a single limb NIV circuit, it is to be attached near the exhalation port. (III A)
- The NIV equipment with all its accessories must be properly disinfected after each use in these patients. While using NIV through a ventilator, mostly there is no airflow back into it, hence, the risk of infection is minimized. However, a bacterial filter and superficial cleaning of the ventilator is advised. (III A)
- High flow nasal cannula (HFNC), another AGP, is preferred over NIV, when used in these patients with hypoxemic failure. However, HFNC has a higher risk of dispersion of aerosol since it does not have a closed circuit.
- Nebulization during HFNC, is recommended to be done either separately after discontinuing HFNC, or simultaneously through HFNC prongs covered with a surgical mask on the face to prevent dispersion of aerosol in the environment. [III A]
- A recommendation on the combined use of nebulization and HFNC is difficult to make in these contagious cases, due to paucity of data, however, both are potentially infectious on their individual use. [III B]
- Health care personnels while nebulizing patients of SARS-CoV-2, SARS-CoV, MERS or other contagious viral infections; whether on mechanical ventilation, NIV or HFNC; must use proper personal protection equipment and follow good aerosol administration practices.[III A]

Q6. Are there any special instructions to be followed while disinfecting the nebulizer following use in SARS-CoV-2 or other contagious infections?

The respiratory secretions (upper and lower respiratory tract) in cases of COVID-19 harbour the SARS-CoV-2 virus which is transmitted by inhalation of bioaerosols derived from it or through the mucosal contact with surfaces and other objects contaminated with it. One milliliter of sputum contains a viral load of approximately 10^8 viral copies.[104] van Doremalen et al., in their experiment have demonstrated the environmental stability of SARS-CoV-2 up to 3 hours in the air post-aerosolization; up to 4 hours on copper; up to 24 hours on cardboard; and up to 2 - 3 days on plastic and stainless-steel surfaces; but, in significantly decreased titres. These findings are comparable with the other results obtained for environmental stability of SARS-CoV-1.[36]

With high infectivity of the patients and long sustainability of the virus, the nebulizer equipment used on the COVID-19 or the other contagious disease patients, is likely to get infected and must be properly cleaned and disinfected after every use to prevent nosocomial infections. Under the ideal conditions, disposable nebulizer units should be used in these patients, to be replaced every 24 hours, or else to avoid cross infection, a single nebulizer unit must be dedicated for use in a particular patient. Reusable jet nebulizers are to be cleaned properly with soap and water, rinsed, disinfected, and air-dried after each therapy. Mesh nebulisers should be cleaned following the manufacturers' guidelines to avoid damage to the equipment and to ensure safety in this patient population.[105]

The SARS-CoV-2 virus can easily be inactivated by heating at a temperature of 56 ° C for 30 minutes; or by using lipid solvents, such as ethanol (>75%), isopropanol (>70%), formaldehyde (>0.7%), povidone-iodine (>0.23%), sodium hypochlorite (>0.21%), or hydrogen peroxide (>0.5%).[106] It has also been observed that ethanol (62–71%), hydrogen peroxide (0.5%) or sodium hypochlorite (0.1%) as disinfectant can effectively reduce coronavirus infectivity within 1 minute and the same effect will also apply to the SARS-CoV-2 also. Other chemical compounds like 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine di-gluconate are relatively less effective.[107] The use of ultraviolet light for 60 minutes also results in the inactivation of several coronaviruses.[106] A study by Duan et al[108] using irradiation with ultraviolet light for 60 minutes on various coronaviruses in the culture medium, resulted in almost undetectable levels of viral infectivity. In another study, Bedell et al,[109] used an automated triple-emitter whole room disinfection system, to inactivate the MHV-A59 and the MERS-CoV viruses on different surfaces, could achieve a greater than 5 log10 reduction on MERS in 5 minutes of UV-C exposure.

While using nebulization in contagious patients, cleaning the nebulizer equipment after each treatment is important. Handwashing must also be undertaken prior to cleaning the equipment. Disinfection of the equipment can be undertaken using heat disinfection methods (electric steam, microwave, dishwasher with hot water and 30-minute wash cycle); or by using disinfecting solutions (70% isopropyl alcohol, 0.5%hydrogen peroxide). The outside of the nebulizer can be wiped clean with 70% alcohol. The surface must be dried thoroughly. Special precautions are needed while cleaning equipment, used by a person with COVID 19, to prevent virus spread. The caregiver should wear a disposable mask and gloves and dispose of them after the treatment in a sealed bag.[110]

Heat Disinfection Methods:

Nebulizer and all other equipment used can be disinfected using a heat method. However, caution should be observed with some plastics which can warp or melt with heat and these may be disinfected with chemical solutions. Any of the following methods using heat can be adopted to disinfect, taking care that it does not damage the equipment. (refer to manufacturer's manual).

- Using an electric steam sterilizer (like a baby bottle sterilizer).
- Boil it for 5 minutes.
- Microwave heating for 5 minutes in a microwavable bag or bowl with water
- Wash in a dishwasher with a 30-minute wash cycle at a temperature >158 degrees.

Disinfection with chemical solutions:

Either of the following solutions can be chosen (with their soaking time) to disinfect nebulizer and other equipments:

- 70% isopropyl alcohol – 5 minutes
- 3% hydrogen peroxide – 30 minutes

The parts of the nebulizer after disinfection should be rinsed in sterile water. Thereafter keep all these on a clean towel and let them dry completely. These should not be stored until completely dry, which may take more than 2 hours in hot and humid weather. The outside of the tubing can be wiped with a moist cloth. If there is water inside the tubing it will take more time and is difficult to dry out. Tubing that becomes dirty from the inside needs to change.

Instructions to be followed by HCP for disinfecting equipment.[111]

- Wear skin and eye protection for potential splash hazards
- Ensure adequate ventilation
- Do not use concentrations and amounts of chemicals more than what are recommended.

- Use water at room temperature for dilution (unless stated otherwise on the label)
- Avoid mixing chemical products
- Label all the diluted cleaning solutions
- Chemicals should be stored out of the reach of children and pets

(Never eat, drink, breathe or inject these products into the body or apply directly to your skin as these can cause serious harm)

Evidence statement:

- Patients infected with contagious viral infections including SARS-CoV-2 transmit infection through bioaerosols generated from their respiratory tract. The survivability of these viruses has been found to be up to 3 hours in air, and variable from few hours to few days on different surfaces, but in decreasing titres, post-aerosolization.
- The nebulizer should ideally be disinfected prior to and after each treatment, in patients with COVID-19 and other contagious viral infections, incorporating the manufacturer's instructions. A single nebulizer unit must be allocated for use in a particular patient to avoid any cross infection. Preference be given to disposable units which should be replaced every 24 hours.
- Coronavirus including SARS-CoV-2 can be disinfected by heating (electric steam sterilizer, boiling-5 min., microwave-5 min., dishwasher with heating-30 min. at 158 degrees); or by soaking in lipid solvents such as ethanol (>75%), isopropanol (>70%); or treating with chemical solutions such as formaldehyde (>0.7%), povidone-iodine (>0.23%), sodium hypochlorite (>0.21%), or hydrogen peroxide (>0.5%). Use of irradiation with ultraviolet light (60 min) can also be done. Detailed instructions for cleaning and disinfection of nebulizer using physical and chemical methods have been provided.
- Healthcare personnel should adopt appropriate infection control practices while cleaning/disinfecting the equipment.

Recommendations:

- The nebulizer used by patients of COVID-19 and other contagious viral diseases are recommended to be cleaned and disinfected, before and after each treatment, by heat or chemical disinfection methods. Irradiation with ultraviolet light can also be done. Equipment manufacturer's instructions also need to be properly followed for the safety of the patient and the equipment. [UPP]
- Preference in these cases is always to be given to disposable nebulizer units which should be replaced every 24 hours. While using regular nebulizer, a single unit must be dedicated for use in a single patient and sharing should be avoided. [UPP]
- Disinfection commonly is recommended by heating using an electric steam sterilizer, boiling, microwave, or dishwasher with heating; or by soaking in lipid solvents or chemicals such as 70% isopropyl alcohol or 3% hydrogen peroxide. Other disinfectants can also be used.[UPP]
- The outer surface of the nebulizer and outside of the tubing can be wiped with alcohol. Replace the tubing if it looks dirty inside.[UPP]
- Nebulizers should be cleaned/disinfected by a caregiver adopting appropriate infection control practices [UPP]

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